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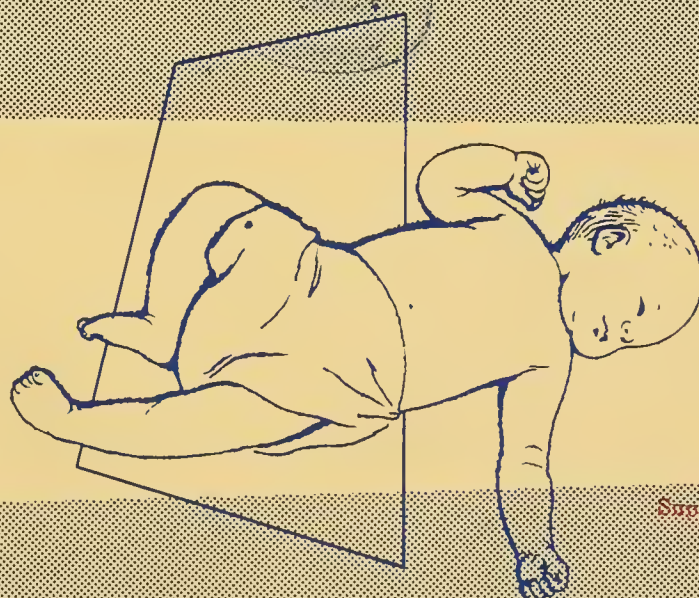
U.S. Children's Bureau

PHENYLKETONURIA

a selected bibliography

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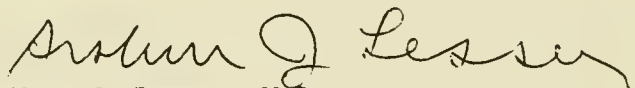
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Phenylketonuria, an inborn metabolic error, is one of the few causes of mental retardation which can be prevented by a specific treatment from exerting its deleterious effects on the central nervous system. In recent years, clinicians, biochemists and geneticists have devoted increasing attention to research on the inheritance pattern, methods of detecting the overt disease and carrier state, biochemical determinations, treatment by dietary management, and experimental production of the disease in animals. This activity has been accompanied by increased interest in other types of metabolic errors.

In order to take note of the most recent research and investigation, the original bibliography on phenylketonuria, issued by the Children's Bureau, has been extended to include reports published in the literature since 1960. A conscientious attempt was made to cover all the major aspects of research on phenylketonuria and select the kind of references that will direct the reader into more intensive study of a given aspect, if he wishes to pursue the subject further. The large body of research published on various aspects of metabolism which has implications for phenylketonuria but no direct bearing, has of necessity been omitted. With a few exceptions, the bibliography does not include reports published in non-English speaking countries nor articles that have appeared in State medical journals.

The listing was prepared by Mrs. Gladys M. Krueger, Program Analyst, Children's Bureau, for public health workers, program planners in the field of mental retardation, and individual practitioners interested in this disorder. Additional copies are available on request from the Division of Health Services, Children's Bureau. Suggestions and comments from its readers will be welcomed as a basis for noting important omissions and correcting inadvertent misinterpretations, and also for evaluating the usefulness of this kind of publication.



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PHENYLKETONURIA - A SELECTED BIBLIOGRAPHY

NOTE: Within each section, references are arranged in the order of their publication dates, beginning with the most recent.

In the General Section, selected key references on the development and understanding of phenylketonuria are marked with an asterisk for the reader who may be using this listing to begin his study of the disease.

GENERAL

Blattner, Russell J.: Phenylketonuria: Phenylpyruvic Aciduria. JOURNAL OF PEDIATRICS, 1961, 59, 294-298 (August).

The author reviews available knowledge regarding phenylketonuria, including a description of the disease, its clinical manifestations, incidence, pathogenetic and biochemical basis, detection and treatment, and the results of studies of experimentally induced phenylketonuria in laboratory animals. He has drawn his material and observations from an excellent selection of references that indicate a careful and selective study of the literature.

Cawte, J. E.: A Note on the Future of Phenylketonuria. JOURNAL OF MENTAL SCIENCE, 1956, 102, 805-811 (October).

The advantages and disadvantages of therapy for persons with phenylketonuria is discussed. The author points out that with the advent of therapy, there will be three instead of two influences maintaining the gene in the population: mutation, greater fertility of the carriers, and direct transmission by phenylketonurics themselves. The progeny from the mating of a phenylketonuric and a non-carrier normal will all be carriers, though having normal phenotypes. Half of the progeny of a phenylketonuric and a carrier will be phenylketonuric, the other half carriers.

Centerwall, Willard R.: Phenylketonuria - A General Review. JOURNAL OF THE AMERICAN DIETETIC ASSOCIATION, 1960, 36, 201-205 (March).

This is an excellent article on phenylketonuria by an author who has made important contributions to knowledge about this disease. His review includes: historical background, incidence, clinical picture, the metabolic defect, treatment and prevention, the diet, and routine detection tests.

Centerwall, Willard R. and Centerwall, Siegfried A.: PHENYLKETONURIA. Children's Bureau Publication No. 388. U. S. Department of Health, Education, and Welfare, Washington, D. C., 1961. 28 pp.

This bulletin is addressed to public health workers and physicians in general practice who are interested in learning about phenylketonuria. The authors provide a comprehensive description of the disease, including its incidence, genetic aspects, biochemistry, and clinical course. They describe the known methods of detecting and managing this disease. They also include practical information, such as laboratory facilities that were equipped and willing, at time of publication, to perform serum phenylalanine determinations, and exchange lists for a low-phenylalanine diet.

Centerwall, Willard R. and Centerwall, Siegfried A.: Phenylketonuria (Fölling's Disease): The Story of Its Discovery. JOURNAL OF THE HISTORY OF MEDICINE AND ALLIED SCIENCES, 1961, 16, 292-296 (July).

The Centerwalls' present the dramatic story of the discovery of phenylketonuria by Dr. Asbjörn Fölling, a Norwegian physician and biochemist. They present highlights of the research he carried out to determine why two siblings, brought to him in 1934, had a peculiar urinary odor. Within 5 months after he saw these children, his intensive research efforts were conclusive enough for him to report on a new metabolic disease which he had identified in 10 cases.

Dr. Fölling has continued to be one of the most significant contributors to the understanding of this disease. In collaboration with his Norwegian colleagues, his other accomplishments include being the first to devise a method of measuring serum phenylalanine levels and thus the first to prove that these levels are high in phenylketonurics; also, the first to demonstrate the increased urinary excretion of certain other metabolites such as phenylactic acid and phenylalanine.

Fölling, Asbjörn: Phenylpyruvic Acid as a Metabolic Anomaly in Connection with Imbecility. ZEITSCHRIFT FÜR PHYSIOLOGISCHE CHEMIE (German), 1934, 227, 169-176.

This is the first recorded description of phenylketonuria in the medical literature. Fölling presents the clinical and physical findings on 10 mentally defective patients who were found to have phenylpyruvic acid in the urine when tested with ferric chloride. Four patients were males, 6 were females, ranging in age from 2 to 20 years. Fölling first used the term "imbecillitas phenylpyruvica" to describe this disorder.

Hsia, David Y-Y.: Recent Developments in Inborn Errors of Metabolism. AMERICAN JOURNAL OF PUBLIC HEALTH, 1960, 50, 1653-1661 (November).

The author discusses current knowledge about inborn errors of metabolism and their potential importance from the public health viewpoint. He uses phenylketonuria as one of his illustrations of an inborn error

of metabolism and provides a detailed description of the pathogenesis of this disease. He stresses the need for early detection and therapy to prevent the need for placing the phenylketonuric child in an institution for the rest of his life.

Jervis, George A.: Phenylpyruvic Oligophrenia. Introductory Study of Fifty Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 1937, 38, 944-963 (November).

Preliminary findings and conclusions are presented for this investigator's intensive study of a group of institutionalized mental defectives with phenylketonuria. Data on these patients include characteristics and personal history; genetic study; constitutional features; neurologic and psychologic manifestations; and some biochemical information.

*Jervis, George A.: Phenylpyruvic Oligophrenia (Phenylketonuria). [In] GENETICS AND THE INHERITANCE OF INTEGRATED NEUROLOGICAL AND PSYCHIATRIC PATTERNS. (Proceedings of the Association for Research in Nervous and Mental Disease, December 11-12, 1953.) Baltimore, Md.: The Williams & Wilkins Company, 1954. pp. 259-282.

This paper is a systematic summary of the knowledge about phenylketonuria available at the time. Dr. Jervis presents a careful and detailed review based on his own findings with some 226 cases and on data accumulated in the literature during 20 years (including 103 cited references).

His review includes information on incidence of the disease among institutionalized defectives; clinical symptomatology; pathological findings; biochemical findings; feeding experiments; genetic aspects; linkage; and treatment.

Kaplan, Arnold R.: Phenylketonuria: A Review. EUGENICS QUARTERLY, 1962, 9, 151-160 (September).

The author provides an extensive review of available knowledge about phenylketonuria including its incidence, clinical manifestations, biochemistry, detection, dietary treatment, and heterozygote determination. His survey of the literature on this disease includes 121 references.

*Knox, W. Eugene, and Hsia, David Y.-Y.: Pathogenetic Problems in Phenylketonuria. Symposium on Inborn Errors of Metabolism. AMERICAN JOURNAL OF MEDICINE, 1957, 22, 687-702 (May).

The mechanisms of pathogenesis are discussed in steps of increasing complexity, from genetics and biochemistry to pathologic physiology and clinical signs. The earlier and simpler phenomena can be thought of as causes of the later and more complex events.

The discussion includes: genetic analysis, gene-protein relationship, signs and symptoms of phenylketonuria, pathogenesis, and treatment.

*Knox, W. Eugene: Phenylketonuria. [In] THE METABOLIC BASIS OF INHERITED DISEASE, edited by John B. Stanbury, James B. Wyngaarden, Donald S. Frederickson. New York: McGraw-Hill Book Co., 1960. pp. 321-382.

Knox's review of phenylketonuria, included as a chapter in the above-cited textbook, is a discerning and balanced assessment of the clinical, biochemical, and genetic information available about this disease up to 1960. The 175 references in the bibliography for this chapter are specifically cited in support of statements and tabulations in the text. This is a superior introduction to the subject of phenylketonuria as well as a comprehensive review for those who are familiar with the disease.

La Du, Bert N.: The Importance of Early Diagnosis and Treatment of Phenylketonuria. ANNALS OF INTERNAL MEDICINE, 1959, 51, 1427-1433 (December).

Recent experience with a low-phenylalanine diet provides convincing evidence that the mental retardation usually associated with phenylketonuria is a preventable consequence of this metabolic disease, provided the treatment is started early. Ideally this would be within the first few weeks after birth. The benefits to be gained by the dietary treatment will be progressively less the longer the child goes without treatment. Although the diet has no effect upon the inherited metabolic defect, it prevents the oligophrenia and the neurologic symptoms found in untreated cases.

The importance of early diagnosis and treatment cannot be overemphasized, and the simple ferric chloride test of the urine should be a routine procedure in young children. Years ago ferric chloride was used in every physician's office to detect acetone bodies, but in recent years this test has been gradually replaced by other methods. It is hoped that physicians will put the bottle of ferric chloride back on their reagent shelf for this new purpose.

*Lyman, Frank L. (Editor): PHENYLKETONURIA. Springfield, Ill.: Charles C Thomas, 1963. 318 pp.

This book is intended to serve as a reference text for scientists interested in phenylketonuria and as a handbook of treatment useful to the practicing physician, dietitian, nurse, social worker and public health worker. Eleven contributors have written on the discovery of phenylketonuria, incidence and inheritance, the clinical features, biochemistry, pathology, pathogenesis of the mental defect, detection, management of phenylketonurics, diets and recipes, tests and reagents, and the experimental approach. There is a bibliography of 641 references.

Mental Deficiency and Phenylketonuria. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 1961, 178, 838 (November 25).

This editorial briefly highlights salient findings and current developments in relation to phenylketonuria, encompassing principal clinical

features, testing methods, and study findings. The conclusion is reached that early detection of phenylketonuria and treatment of the disease in young infants offer a reasonable chance of preventing mental retardation.

Shaw, Kenneth N. F.; Koch, Richard; Schild, Sylvia; Ragsdale, Nancy; Fishler, Karol; Acosta, Phyllis B.: THE CLINICAL TEAM LOOKS AT PHENYLKETONURIA. Children's Bureau, U. S. Department of Health, Education, and Welfare, Washington, D. C., 1961. 30 pp.

Problems of phenylketonuria are presented from the viewpoint of the biochemist, pediatrician, medical social worker, public health nurse, psychologist, and nutritionist. The contributions of the foregoing disciplines are all important in the proper management of this disease. The presentations by a multidisciplinary team working with phenylketonuric children alert the reader to the many problems encountered in providing guidance to their families.

Treatment of Phenylketonuria. Report to the Medical Research Council of the Conference on Phenylketonuria. BRITISH MEDICAL JOURNAL, 1963, 5347, 1691-1697 (June 29). Reprinted in pamphlet form by the British Medical Association, Tavistock Square, London, 1963. 20 pp.

In 1960 a Conference on Phenylketonuria was called by the Medical Research Council to consider the practical problems of detection, early treatment, and subsequent care of children with this disorder. Among the 20 members of the Conference were public health administrators, pediatricians, psychiatrists, psychologists, biochemists, geneticists, and others, all with first hand experience of some of the problems of phenylketonuria. They met in London at intervals over the past 3 years.

The report of the Conference contains recommendations on optimum times and methods of testing for this condition, and a note on the fallacies which may be encountered. Details are given on methods of control of treatment recommended for general use, and on diets which can be used in the treatment of phenylketonuria without prejudicing normal growth and development in the early months of life. A brief review is also provided of results of treatment in infants.

Udenfriend, Sydney: Phenylketonuria. AMERICAN JOURNAL OF CLINICAL NUTRITION, 1961, 9, 691-694 (November-December).

In this perceptive presentation, the author graphically presents the chemical changes associated with phenylketonuria. He evaluates the results of investigations which focus on various aspects of phenylalanine metabolism and which offer hypotheses regarding possible mechanisms of interference with normal mental development.

There is a brief discussion of the therapeutic and diagnostic aspects of this disorder, and the chemical tests that make it possible to distinguish a group of heterozygous carriers of phenylketonuria from a normal group of non-carriers. The author also points out that recent

success with an experimental animal should prove of great importance in corroborating present concepts of the disease and in exploring the chemical pathology of the central defect.

Wright, Stanley W., and Tarjan, George: Phenylketonuria. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1957, 93, 405-419 (April).

This is a review of the literature on phenylketonuria and a report of 21 patients with this disorder. It includes a review of the history, clinical findings, incidence, genetics, biochemistry, clinical laboratory studies, pathology, and treatment.

Unexplained features of the disease include: the presence of psychological abnormalities associated with a metabolic deficit; the relationship between the mental defect and the metabolic aberrations; the possible occurrence of the disease among the normal, the less retarded, and the psychotic population; and finally, the role of tryptophane abnormalities in relation to the clinical manifestations of the disease.

METHODS OF DETECTION AND DIAGNOSIS

Baird, Henry W., III: A Reliable Paper-Strip Method for the Detection of Phenylketonuria. JOURNAL OF PEDIATRICS, 1958, 52, 715-717 (June).

A paper-strip method for detection of phenylketonuria has been found reliable and practical. Its routine use at the time of the first and second well baby visit is suggested. The test should be repeated in any infant whose mental development is slow.

Berry, Helen K.: Paper Chromatographic Method for Estimation of Phenylalanine. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1957, 95, 71-73 (May).

For paper chromatographic estimation of phenylalanine, 10.5 ml. samples of blood serum are deproteinized with 4 volumes of 95 percent ethyl alcohol and the filtrate used for preparation of the chromatogram. The method is especially useful in study of phenylketonuric infants, and in following the changes in serum phenylalanine when a low-phenylalanine diet is used for their treatment.

Berry, Helen K.; Sutherland, Betty; Guest, George M.; and Warkany, Joseph: Simple Method for Detection of Phenylketonuria. JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 1958, 167, 2189-2190 (August 30).

This article describes a simple method for detection of phenylketonuria by the collection of urine on filter paper, which is then tested for the presence of phenylpyruvic acid.

Berry, Helen K.: Procedures for Testing Urine Specimens Dried on Filter Paper. CLINICAL CHEMISTRY, 1959, 5, 603-607 (December).

Procedures are described for testing for phenylpyruvic acid, sugars, protein, and chondroitin sulfuric acid in urine dried on filter paper. Additional paper chromatographic methods for identification of phenylalanine, o-hydroxyphenylacetic acid, glucose, and galactose are described.

Berry, Helen K.: Detection of Metabolic Disorders Among Mentally Retarded Children by Means of Paper Spot Tests. AMERICAN JOURNAL OF MENTAL DEFICIENCY, 1962, 66, 555-560 (January).

Urine specimens dried on filter paper were obtained from 700 mentally retarded children in foster homes and public and private child care agencies in Ohio. These specimens were tested for the presence of 11 substances, each of which may be present in increased amounts in urine of children with a given metabolic disorder. Three children with phenylketonuria were detected. (Thirteen children with other metabolic disorders were identified.) These spot tests offer a simple and inexpensive approach for mass screening procedures to be applied either to mentally retarded children, to institutional populations, or to newborn infants.

Berry, Helen K.: Use of Micromethod for Phenylalanine in Management of Phenylketonuric Patients. CLINICAL CHEMISTRY, 1962, 8, 172-173 (April).

The author describes a micromethod for measurement of blood phenylalanine which meets the need for frequent and rapid determinations and keeps the amount of blood required for repetitive determinations to a minimum.

This method is not proposed as a substitute for the more exact procedures for measuring phenylalanine concentrations in blood from non-phenylketonuric individuals. However, it does provide a means for distinguishing quickly between the phenylketonuric and nonphenylketonuric individual. The procedure is most useful in management of phenylketonuric children under treatment for whom it is essential to determine the effectiveness of the dietary regimen.

Centerwall, Willard R., Chinnock, Robert F., and Pusavat, Albert: Phenylketonuria: Screening Programs and Testing Methods. AMERICAN JOURNAL OF PUBLIC HEALTH, 1960, 50, 1667-1677 (November).

Six tests for phenylketonuria are outlined and the advantages and disadvantages of each test are discussed. The tests described are (1) test-tube test with ferric chloride, (2) diaper test with ferric chloride, (3) Phenistix (dipstick) test, (4) filter-paper test with ferric chloride, (5) dinitrophenylhydrazine test-tube test, and (6) serum phenylalanine determination. The first five of these are simple urine tests. The second, third and fourth tests are particularly suitable for mass well-baby screening programs.

All the tests studied were found to be comparable in accuracy and each test has enough specific merits to make it particularly valuable under certain circumstances. The maximum value of each type of test is dependent on some simple but specific precautions and knowledge essential to the reliability of the test. Most of these vital factors are included in the discussions of the respective tests.

Three organized screening programs for the detection of infant phenylketonurics within "normal, well-baby" populations are briefly described. Each of these programs, from widely separated geographic areas (California, England, Cincinnati, Ohio) uses a different method of testing. The hospital newborn nursery is not a suitable place to screen for phenylketonuria by use of any urine test because phenylketonuric infants rarely give positive urine tests until after the first week of life.

NOTE: An adaptation of this paper appears in Chapter 7: Detection-Testing Methods. In PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 123-130).

Culley, W. J.; Mertz, E. T.; Luce, M. W.; Calandro, J. M.; Jolly, D. H.: Paper Chromatographic Estimation of Phenylalanine and Tyrosine Using Finger-Tip Blood. Its Application to Phenylketonuria. CLINICAL CHEMISTRY, 1962, 8, 266-269 (May-June).

It is desirable that a method for measuring serum phenylalanine should be simple and rapid, use small quantities of blood, and require only equipment found in the average clinical laboratory. The authors describe a paper chromatographic method for the determination of serum phenylalanine and tyrosine that can be performed in 20 minutes working time, requires only 0.12 ml. of serum, no deproteinization, and no expensive equipment.

Results of experimental application of this method to detect phenylketonuria and to check serum phenylalanine levels of phenylketonurics on low-phenylalanine diets, are presented. Observations are made regarding particular laboratory procedures and techniques that should be followed for efficient use of this method.

Fellman, J. H.: Detection of Phenylpyruvic Oligophrenia. JOURNAL OF NERVOUS AND MENTAL DISEASE, 1956, 123, 575 (June).

The author calls attention to the inadequacy of employing ferric chloride alone as a diagnostic reagent in testing for phenylketonuria.

In a survey of 1,700 institutionalized mental defectives, 23 patients gave a positive reaction to the ferric chloride reagent. When subsequent confirmation of the presence of phenylpyruvic acid in their urine was attempted using 2,4-dinitrophenylhydrazine, only 21 of the 23 gave a positive test. Further examination of the false positive reactions revealed that the ferric chloride reaction was due to the presence of a metabolite of the drug, chlorpromazine and not to phenylpyruvic acid. Because of the increasingly prominent role this drug is playing in psychiatric medication, attention should be given to the foregoing findings when screening mental defectives for phenylketonuria.

Gibbs, N. K. and Woolf, L. I.: Tests for Phenylketonuria. Results of a One-Year Programme for Its Detection in Infancy and Among Mental Defectives. BRITISH MEDICAL JOURNAL, 1959, 5151, 532-535 (September 26).

A program aimed at testing the urine of all infants for phenylketonuria who were born in Cardiff achieved only a 25 percent success. One case was detected and treated successfully. Since it is difficult to get a suitable specimen of urine, a simpler test in which a wet napkin can be used is necessary.

A new test strip, Phenistix, is a simpler and quicker method of testing urine for phenylpyruvic acid than methods hitherto used. It may

also provide a partial answer to the problem of testing on the napkin. Unlike ferric chloride and 2,4-dinitrophenylhydrazine, it does not give a false-positive reaction with p-hydroxyphenylpyruvic acid, which was found in the urine of a number of infants in the Cardiff survey.

Guest, George M.; Berry, Helen; and Rubinstein, Jack H.: MANAGEMENT OF NEWBORN SIBLINGS OF PATIENTS WITH PHENYLKETONURIA OR GALACTOSEMIA. Children's Bureau, U. S. Dept. of Health, Education, and Welfare, 1962. 15 pp.

Recommended diagnostic procedures are fully described for detection of phenylketonuria or galactosemia in newborn siblings born in families known to have these hereditary disorders.

Questionnaires were sent to 23 physicians who have had experience in dealing with phenylketonuria and galactosemia, asking them to give their recommendations on specific aspects of the management of newborn siblings of affected patients. Replies received from 18 of them are summarized in tabular form. Another table presents preventable forms of mental retardation classified by disease and treatment.

Guest, George M.; Berry, Helen K.; and Rubinstein, Jack: Newborn Siblings in Families Known to Have Hereditary Disorders. Diagnostic Procedures. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 1962, 181, 439-440 (August 4).

Early detection, followed by prompt and careful treatment, may prevent the severe mental retardation usually associated with cases of phenylketonuria and galactosemia. It is particularly important that knowledge gained by research workers be brought to the attention of physicians who may first come in contact with the affected children. Both conditions are inherited as a recessive trait. The risk to subsequent siblings in a family in which the disease is known to be present is one chance in four, in contrast to the relatively low incidence in the general population. Diagnostic procedures are described.

Guthrie, Robert and Tieckelmann, Howard: The Inhibition Assay: Its Use in Screening Urinary Specimens for Metabolic Differences Associated with Mental Retardation. PROCEEDINGS OF THE LONDON CONFERENCE ON THE SCIENTIFIC STUDY OF MENTAL DEFICIENCY, July 1960. pp. 672-677.

The principle of "biochemical antagonism" between two substances is used to determine the presence or absence of one antagonist in a specimen by introducing the specimen into a culture of micro-organism whose growth is being inhibited by the presence of the other antagonist. A new test for the level of phenylalanine in serum or urine uses Bacillus subtilis inoculated into a sucrose-salts agar medium supplemented by Beta-2-thienylalanine which inhibits growth of the organism. In this "inhibition assay," filter paper discs impregnated with 0.01

milliliter of the serum specimen and discs impregnated with different concentrations of phenylalanine are incubated in the medium. The diameter of the growth around the specimen-impregnated discs as compared with that around the discs with specified concentrations of phenylalanine provides a measure of concentration in the serum.

Blood obtained from a heel puncture and drawn in capillary tubes is adequate for the small sample required for this assay. The authors consider this an advantage for daily blood assays in small infants and a convenient system for following blood levels of phenylalanine during initiation of a phenylalanine restricted diet.

The existence of biochemical antagonism between many substances, natural and synthetic, offers the possibility of delineating other biochemical abnormalities associated with human disease. Some of those being investigated by the authors are described.

Guthrie, Robert: The Inhibition Assay: A Method for Detecting Chemical Differences in Clinical Specimens. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1961, 102, 583-584 (October).

The author discusses the principle of the inhibition assay and its potential uses. With use of *B. subtilis* inhibited by Beta-2-thienylalanine, a unique substance (TA factor) was found in urine from cases of oculocerebrorenal syndrome (Lowe's syndrome). This TA factor also was found in 8 out of 13 urine specimens from untreated patients with phenylketonuria. It was discovered that each of 30 newborn infants excreted this substance in amounts approaching the equivalent of 1 mg. of phenylalanine per milliliter of urine. The TA substance was not present, however, in 150 specimens from healthy children 3 years of age or older, as well as several hundred specimens from children with miscellaneous central nervous system abnormalities, especially mental retardation. The TA substance also was absent from urine specimens obtained from a young infant with phenylketonuria.

The thienylalanine inhibition assay has been used for estimation of daily blood phenylalanine levels in 14 phenylketonuric children during hospitalization for initiation of dietary treatment (Children's Hospital, Buffalo).

Hsia, David Yi-Yung; Litwack, Marcia; O'Flynn, Margaret; and Jakovcic, Smilja: Serum Phenylalanine and Tyrosine Levels in the Newborn Infant. NEW ENGLAND JOURNAL OF MEDICINE, 1962, 267, 1067-1070 (November 22).

This research was undertaken to determine the precise levels of both phenylalanine and tyrosine in the serum of full-term and premature infants. It was found that full-term infants showed normal phenylalanine and slightly elevated tyrosine levels. In contrast, premature infants showed moderate increases in phenylalanine and marked increases

in tyrosine levels. The phenylalanine and tyrosine levels were closely correlated in the premature infant, but were unrelated in the full-term infant. By the use of this quantitative method, it was possible to find elevated phenylalanine levels in two phenylketonuric children as early as the second day of life.

The demonstration of normal serum phenylalanine levels in full-term newborn infants provides an easy baseline for screening procedures for phenylketonuria. To ensure greater sensitivity and accuracy, it is recommended that screening should be undertaken with the use of quantitative procedures for phenylalanine. In routine screening of newborn infants, it is ordinarily unnecessary to run the tyrosin level. The application of the present methods to mass surveys is currently being investigated.

La Du, Bert N., and Michael, Patricia J.: An Enzymatic Spectrophotometric Method for the Determination of Phenylalanine in Blood. JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 1960, 55, 491-496 (March).

A simple enzymatic spectrophotometric method has been described for the quantitative determination of phenylalanine in serum. The method is based upon the measurement of the absorption of the enol-borate complex of phenylpyruvic acid generated enzymatically from phenylalanine by L-amino acid oxidase of snake venom. For elevated serum levels of phenylalanine the method is rapid, specific and precise. It should be useful as a confirmatory test in the diagnosis of suspected phenylketonuria and in the evaluation of the effectiveness of a diet low in phenylalanine. The values obtained by this method agree well with those in the literature obtained by other techniques. Tyrosine and tryptophan are also determined by this method, and a suitable modification of the method is described which should allow an accurate estimation of these amino acids and phenylalanine in normal serum.

La Du, Bert N.; Howell, R. Rodney; Michael, Patricia J.; and Sober, Eva K.: A Quantitative Micromethod for the Determination of Phenylalanine and Tyrosine in Blood and Its Application in the Diagnosis of Phenylketonuria in Infants. PEDIATRICS, 1963, 31, 39-46 (January).

The enzymatic spectrophotometric method to determine phenylalanine and tyrosine concentrations in serum, developed by La Du and Michael (JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 1960, 55, 491-496, March 1960) has been modified so that it may be used with small amounts, 0.1 milliliter, of whole blood. This modification makes it possible to determine accurately both phenylalanine and tyrosine in very young babies, using heel prick samples. Procedures for carrying out this method are fully described. Analytical results of its application on a group of premature and full term infants are discussed. Findings showed that normal infants have a broader range of blood phenylalanine values than adults, and that tyrosine levels may be as high as 20 mg./100 ml. in older infants and prematures. The fact that transient elevation of blood phenylalanine may occur

in normal newborn infants must be taken into careful consideration before making a diagnosis of phenylketonuria in early infancy.

Mabry, C. Charlton; Nelson, Thomas L.; Horner, Frederick A.: Occult Phenylketonuria. CLINICAL PEDIATRICS, 1962, 1, 82-86 (November).

This is a case report on an infant with phenylketonuria diagnosed at the age of 6 months, for whom the urine ferric chloride test was never positive. Because an older sibling was known to have phenylketonuria, this infant was tested by Phenistix in the first, second, and fourth months of life with no positive reaction. At four months, a serum phenylalanine determination showed an unexpected elevated level, though only moderately. Further clinical findings and observations supported the diagnosis of phenylketonuria.

The authors discuss some of the problems concerning diagnosis of this disease and the implications of their findings for mass detection programs. They suggest the need for other diagnostic procedures in addition to the urine test for infants with a family history of phenylketonuria.

McCaman, Marilyn W. and Robins, Eli: Fluorimetric Method for the Determination of Phenylalanine in Serum. JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 1962, 59, 885-890 (May).

The authors report their development of a fluorimetric method for the determination of phenylalanine in serum which requires as little as five microliters of serum -- markedly less than the amount required by other currently available quantitative methods. The fluorimetric determination of phenylalanine is based on the enhancement of the fluorescence of a phenylalanine-ninhydrin reaction product by a peptide, leucylalanine. The method measures phenylalanine down to extremely small amounts (approximately one one-hundredth of a microgram) in the presence or absence of other amino acids. Procedures for carrying out the method are described. The results of its application to the determination of phenylalanine serum levels in adult, pediatric, and phenylketonuric patients are presented. The values found are in good agreement with those reported in the literature using other methods.

O'Brien, Donough and Ibbott, Frank A. (editors): LABORATORY MANUAL OF PEDIATRIC MICRO- AND ULTRAMICRO-BIOCHEMICAL TECHNIQUES. New York: Harper and Row, 1962. 500 pp. (p. 242-244).

This manual, which encompasses the micro-methods currently used in pediatric clinical chemistry, includes a section on the methods for "Determination of Phenylalanine, Tyrosine, and Tryptophan in Serum and Other Biological Fluids". A commentary discusses the clinical relevance of serum phenylalanine levels as a means of detecting phenylketonuria in the newborn infant significantly before phenylpyruvic acid is detectable in urine by the ferric chloride test.

Two methods are recommended, preferably the first, for diagnostic confirmation and dietary control: (1) Fluorimetric assay (McCaman-Robins, with modifications); (2) Enzymatic assay (LaDu-Michael, with modifications). The procedures and calculations necessary to carry out each method are described.

The tests described for determining phenylpyruvic acid in urine are: (1) 10 percent ferric chloride, (2) Phenistix, and (3) dinitrophenylhydrazine.

Scheel, Carolyn and Berry, Helen K.: Comparison of Serum Phenylalanine Levels with Growth in Guthrie's Inhibition Assay in Newborn Infants. JOURNAL OF PEDIATRICS, 1962, 61, 610-616 (October).

A study is reported which compares the results of measurements of whole blood phenylalanine by the Guthrie inhibition assay with those obtained by established procedures for phenylalanine (including enzymatic spectrophotometric method and paper chromatography). Blood from newborn infants, from patients with treated and untreated phenylketonuria, and from animals with experimental phenylketonuria was tested. Results obtained by the inhibition assay were consistently higher than those obtained by other methods. The inhibition procedure measures substances unrelated to phenylalanine. The authors conclude that the inhibition method, with the use of whole blood, is probably not sensitive enough for use as a test for detection of phenylketonuria in a nursery for newborn infants.

Veal, A. R.: Phenylalanine O-Hydroxyphenylacetic Acid. Phenylpyruvic Acid -- Phenylketonuric Diagnosis. A Report of Study Made on 77 Students in Schools for Mentally Retarded. AMERICAN JOURNAL OF MEDICAL TECHNOLOGY, 1961, 27, 191-196 (July-August).

A simple clinical laboratory procedure employing paper chromatography for a positive identification of phenylketonuria is described, based on the technique of testing for three possible abnormal metabolites found in the urine of these individuals. Evidence is presented to substantiate further confirmatory tests after a positive or doubtful screening test has been obtained.

Woolf, L. I.: Tests for Phenylketonuria. CEREBRAL PALSY BULLETIN, 1961, 3, 249-254 (June).

The author describes various tests for phenylketonuria and presents his views on when and whom to test for this disease. To be fully effective treatment must be started within a few weeks of birth, before any clinical signs appear. Therefore, the urine of all babies should be tested for phenylpyruvic acid so that, in affected infants, treatment can be started as early as possible. Positive cases should have the diagnosis confirmed by a laboratory with the least possible delay before treatment is started. It is best to test twice, at two weeks and at six weeks of age. If only one test is possible, three to four weeks is the best compromise.

In addition to the newborn, all mentally retarded, psychologically disturbed, or epileptic children should have their urine tested for phenylpyruvic acid. The information obtained is necessary for genetic counselling. Also, older phenylketonuric children are often improved, to some extent, by a low-phenylalanine diet.

Woolf, L. I.: Tests and Reagents. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 251-264).

The biochemical procedure used for detecting or diagnosing phenylketonuria depends on whether the objective is large-scale mass survey or laboratory confirmation of a suspected case. For the former group, ease of application and economy are major considerations. For the second group, reliability is most important. Phenylpyruvic acid is unstable, especially in urine on a diaper on a hot day. Ferric chloride solution is less convenient and less specific than Phenistix strips; 2,4-dinitrophenylhydrazine is a sensitive but relatively non-specific test. Diaper tests can be carried out by public health nurses in the field (i.e. the home or well-baby clinic). The filter paper test of Berry et al. involves examination in a central laboratory with its accompanying advantages and disadvantages. This also applies to the Guthrie technique.

Five techniques are described that are valuable in the quantitative determination of phenylalanine in blood, essential for confirmation of suspected phenylketonuria and also for the regulation of dietary phenylalanine intake during treatment. Paper chromatography is simple and the accuracy, though low, is adequate for diagnosis and dietary control. Microbiological assay of phenylalanine gives an accuracy of 12-15 percent. Enzymatic decarboxylation is troublesome and very sensitive to variations in technique, but can give considerable accuracy provided meticulous care to keep conditions standard is exercised at every stage. The Kapeller-Adler reaction also requires careful standardization of technique and may give erroneous results. The snake venom L-amino acid oxidase method (La Du-Michael) promises to prove the best from the standpoint of simplicity and accuracy. The author uses an ultrafiltrate of serum (modification of La Du-Michael) and finds this very satisfactory. A full account of this modification will be published. (L. I. Woolf and B. L. Goodwin: "Determination of Phenylalanine in Blood and Urine", in preparation.)

Phenylpyruvic acid in urine can be determined quantitatively either with ferric chloride after ethereal extraction or with 2,4-dinitrophenylhydrazine. Paper chromatographic detection of o-hydroxyphenylacetic acid is a complete diagnostic test for phenylketonuria.

Wortis, Joseph, and Giancotti, Antonio M.: A New Simple Test Paper for Mass Detection of Phenylketonuria. AMERICAN JOURNAL OF PUBLIC HEALTH, 1959, 49, 463-464 (April).

The authors present a rapid screening test for the detection of phenylketonuria. Small strips of prepared paper may be used by immersion in a fresh urine specimen or by simple pressure against a wet diaper. This simple method can be used for surveys of large populations.

Allen, Richard J.: The Detection and Diagnosis of Phenylketonuria.
AMERICAN JOURNAL OF PUBLIC HEALTH, 1960, 50, 1662-1666 (November).

This paper presents the experience of the University of Michigan pediatric clinic with the detection and diagnosis of phenylketonuria. Included are the results of an organized Statewide survey in the high-risk population which identified 45 patients with this condition, and description of a "PKU Kit" devised by the clinic for use in its routine testing program.

The author suggests a "cross-checking" system between the family physician, pediatric clinic, and State institutions so that in all routine infant examinations and in the evaluation of neurologically defective children, testing the urine for phenylpyruvic acid will always be done. A systematic procedure of testing could eventually result in identification of every case of phenylketonuria in a given area through the establishment of a central registry. In the University of Michigan pediatric clinic, use of phenylketonuria survey cards filled out by directors of State institutions, local physicians, and clinic staff members permits rapid estimation of number of cases, location of patients, familial incidence, degree of intellectual impairment, and number under treatment.

Berry, Helen K.; Sutherland, Betty S.; and Guest, George M.: Detection of Metabolic Disorders Among Young Infants: A Case-Finding Program.
AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1960, 100, 570-571 (October).

A case-finding program to detect phenylketonuria was begun in Cincinnati in 1958. About 20,000 urine test kits were distributed to mothers of newborn infants -- 16,000 through maternity sections in hospitals. Of the 7,000 specimens returned for testing, none were positive for phenylpyruvic acid.

Urine specimens from 350 mentally retarded children were collected on filter paper squares. Of this group, 9 were positive for phenylpyruvic acid.

Berry, Helen K.; Sutherland, Betty S.; and Guest, George M.: Cincinnati Phenylketonuria Detection Program -- A Progress Note. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 1961, 178, 842 (November 25).

These investigators report one positive test result after testing 10,500 specimens of urine (large scale detection program begun in 1958 using filter paper urine test kits). This was a 5-week-old infant who was promptly placed on a low-phenylalanine diet when diagnosis was confirmed by serum phenylalanine determination. At age 9 months, the child appears to be developing normally, both physically and mentally.

Procedures for carrying out this detection program have proven satisfactory. Kentucky and Wisconsin are reported as having begun similar infant testing programs on Statewide basis. California also is testing infants for phenylketonuria, using wet diaper test with ferric chloride as a reagent.

Boyd, Mary M. M.: Phenylketonuria: City of Birmingham Survey. BRITISH MEDICAL JOURNAL, 1961, 5228, 771-773 (March 18).

The author describes the organization of a screening survey for phenylketonuria covering 98.8 percent of infants at 6 weeks of age who were born in 1959 and living in a county borough. Results demonstrate that the use of Phenistix is a practicable method for screening of young infants. The incidence of cases was that expected, namely about 1 in 20,000.

Intermittent true but weak positive results may recur in children who develop normally. The occurrence of this phenomenon in an infant whose development apparently proceeded normally is recorded.

Centerwall, Willard R.; Berry, Helen K.; and Woolf, L. I.: Chapter 7: Detection. In PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 114-135).

Programs for detection of all cases of phenylketonuria among the newborn and among mentally retarded children in California, Ohio and Great Britain are described. In Great Britain 87 percent of local health authorities are running such screening programs. The practical and administrative problems are described and discussed.

Deisher, Robert W.; Balkany, Andrew F.; Prewitt, Charles D. and Redfield, William J.: Phenylketonuric Families in Washington State. A Survey. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1962, 103, 818-821 (June).

Families known to have children with phenylketonuria (61 known cases in State of Washington) were contacted in order to inform them regarding the possibility of further children having the disease. Forty-one homes were visited and information was given regarding the importance of early detection and the value of dietary management. Local health departments and private physicians were also contacted and given information regarding these families. A register of all families was established and is being operated by the State Department of Health.

Farquhar, James W.; Kansas, Eugenia T.; Tait, Haldane P.: Problems of Routine Screening for Phenylketonuria. LANCET, 1962, 2, 498-500, (September 8).

In Edinburgh, Scotland, beginning in 1960, routine screening for phenylketonuria was carried out on 98.2 percent of all newborn infants at age 6 weeks. Phenistix was test administered by visiting health

nurses. No new cases were reported as a result of this screening. The only new case found, the younger sibling of a phenylketonuric patient, had a negative diaper test at 6 weeks and again at 8 months, when the older child was diagnosed as having phenylketonuria. But fresh urine voided and tested at the clinic gave a positive Phenistix result for the 8-month-old infant, with subsequent confirmation of diagnosis by an abnormally high serum phenylalanine level.

In spite of all the screening work which had been done, this case -- which, on the basis of the average number of livebirths per year in Edinburgh, could be the only new case of phenylketonuria over a $2\frac{1}{2}$ year period -- had escaped detection. Therefore, it was decided to investigate both the methods by which human error could be reduced and those factors which might interfere with the detection of that one case in 20,000 (the generally accepted frequency). By experimenting with procedures for reducing possibilities of error, a "paper-tissue" method of collecting urine specimens was developed with the recommendation that testing results should be determined at a central point, such as the local health department, by a qualified person, under specified conditions.

FOUR SURVEYS OF PHENYLKETONURIA HIGH RISK GROUPS. Children's Bureau, U. S. Dept. of Health, Education, and Welfare, Wash., D.C., 1961. 14 pp.

This publication includes four articles that illustrate different approaches to phenylketonuria screening of high risk groups, such as persons in institutions and children in special classes for the mentally retarded. Once families with a history of phenylketonuria are identified, all present and future siblings can be tested, thus leading to early diagnosis of the disease, especially in newborn infants. The articles include:

Centerwall, Willard R. and Chinnock, Robert F.: Phenylketonuria. Report of a Survey to Discover Treatable Siblings of Institutionalized Patients. MEDICAL ARTS AND SCIENCES, 1959, 13, 173-175 (December).

Centerwall, Willard R. and Chinnock, Robert F.: Phenylketonuria. Replies from a Letter to Institutions for the Mentally Retarded. MEDICAL ARTS AND SCIENCES, 1961, 15, 5-7 (First Quarterly).

Henderscn, Robert A. and Centerwall, Willard R.: Exceptional Children: A Pilot Study for Detecting Phenylketonuria in Public School Children. Published under title: The Attack on Phenylketonuria; A Pilot Study. EXCEPTIONAL CHILDREN, 1961, 27, 260-263 (January).

Deisher, Robert W.: Survey of Phenylketonuria Families in Washington State. Written specifically for the Children's Bureau.

Frazier, Robert L.: Phenylpyruvic Amentia (A Report of An Institution Survey). AMERICAN JOURNAL OF MENTAL DEFICIENCY, 1947, 51, 577-586 (April).

The results of a survey for the detection of phenylketonuria at Orient State School, Orient, Ohio, are presented. Out of 3,000 examinations, 10 positive cases were found. Data were obtained on family histories, in some cases four generations, of the positive cases. The author concludes that phenylpyruvic amentia can be classified within the broader group of hereditary metabolic disorders.

Garfield, Sol L. and Carver, Michael J.: Phenylketonuria: A Further Study. JOURNAL OF NERVOUS AND MENTAL DISEASE, 1960, 130, 120-124 (February).

This is a study of 20 phenylketonuric patients at the Beatrice State Home in Nebraska. Their age at time of admission ranged from about 3 to 65. Only one was originally diagnosed as phenylketonuric. The remainder were institutionalized as mentally defective with varying diagnoses. The authors report the results of their study and compare them with previous findings in the literature. In general these comparisons show no significant differences.

Harding, W. G. and Shaddick, C. W.: Phenylketonuria. A Pilot Screening Survey in London. MEDICAL OFFICER, 1961, 106, 51-53 (July 21).

The possibility of the prevention or amelioration of mental sub-normality associated with phenylketonuria, if diagnosed and treated sufficiently early, has led a number of local health authorities to carry out tests on a wide scale. In London it was decided to conduct a pilot survey to establish the practicability of routine testing of all infants for phenylketonuria and the amount of extra effort by health visiting staff which would be required.

The organization of a pilot screening survey for phenylketonuria using two tests and covering 530 babies born to residents of one area of London during six months ended April 1960, is described. Analysis of results shows age, place of tests, by whom they were read, and difficulties of obtaining complete coverage. Number of tests and of special visits or appointments, and the action necessary to avoid defaulters are discussed together with suggestions for alternative (selective) methods of screening.

Mellon, J. P.: The Diagnosis of Phenylketonuria. SCOTTISH MEDICAL JOURNAL, 1961, 6, 426-427 (September).

A survey of phenylketonuria using Phenistix was carried out on 828 mental defectives consisting of inmates of mental deficiency hospitals and pupils at a special school and at an occupational center. The diagnosis in 4 known patients was confirmed and 11 new patients were discovered. The simplicity of the method used and the reliability of the test strip for the detection of phenylketonuria were demonstrated.

Munro, T. A.: Phenylketonuria: Data on 47 British Families. ANNALS OF EUGENICS, 1947, 14, 60-88 (October).

This paper presents a detailed analysis, including statistical tabulations and the individual family pedigrees and clinical histories, of 47 families studied. In this series, there were 74 proven cases of phenylketonuria and 12 other mentally defective children who died before examination but who probably also were affected.

Paine, Richmond S.: The Variability in Manifestations of Untreated Patients with Phenylketonuria (Phenylpyruvic Aciduria). PEDIATRICS, 1957, 20, 290-302, (August).

This article presents a study of 106 cases of phenylketonuria surveyed in 11 institutions in New England and Quebec, Canada. The analysis includes: patient material and methods, age and sex, developmental history, seizures, EEG, family history, physical characteristics, and range of intelligence. This survey will be of significant usefulness in comparative evaluation of results with treated patients on low-phenylalanine diets.

Partington, M. W.: Observations on Phenylketonuria in Ontario. CANADIAN MEDICAL ASSOCIATION JOURNAL, 1961, 84, 985-991 (May 6).

Data are presented showing age, sex and racial distribution, geographical location and mortality of 98 patients with phenylketonuria from Ontario. By current estimates of the incidence of the disease, the 83 living patients in the series represent about one-third of the province's phenylketonuric population.

The age distribution of the patients suggests that untreated phenylketonuria has an increased mortality rate but that this is no higher than that associated with mental defect in general. There is some evidence that a history of infantile eczema worsens the prognosis.

Phenylketonuria is reported in an apparently pure-blood Ojibwa Indian with brown skin and very dark brown eyes. Several other patients had dark hair. This emphasizes the fact that, although phenylketonurics have lighter-colored hair than other members of their families, fair hair and blue eyes are not essential to the clinical picture and are of little diagnostic value.

The corrected ratio of patients affected with phenylketonuria to their unaffected siblings agreed closely with the ratio of 1 to 3 expected in a recessively inherited disorder.

Suggestions are presented as to where the remainder of the phenylketonuria cases in the province may be sought and the importance of locating them for treatment, for testing of all present and future siblings, thus leading to an early diagnosis of the disease in others.

Armstrong, Marvin D., and Tyler, Frank H.: Studies on Phenylketonuria. I. Restricted Phenylalanine Intake in Phenylketonuria. JOURNAL OF CLINICAL INVESTIGATION, 1955, 34, 565-580 (April).

Five children with phenylketonuria have been given synthetic diets deficient in phenylalanine. Blood phenylalanine levels were lowered to normal values, phenylpyruvic acid excretion ceased, and abnormal excretion of other metabolites ceased. The hypothesis is advanced that the diet overcomes the effects of some substance toxic to the central nervous system. To prevent irreversible damage to the central nervous system, the diet should be started at as early an age as possible.

Armstrong, Marvin D.; Low, Niels L.; and Bosma, James: Studies on Phenylketonuria. IX. Further Observations on the Effect of Phenylalanine-restricted Diet on Patients with Phenylketonuria. AMERICAN JOURNAL OF CLINICAL NUTRITION, 1957, 5, 543-554 (September-October).

Twelve cases of phenylketonuria treated with diets low in phenylalanine are presented. Dietary management, clinical procedures and results of treatment are discussed. Results available indicate that children under two to three years old may be remarkably benefited by dietary treatment. Results in older children are difficult to evaluate. The occasional improvement noted may be due to relief of neurological manifestations, such as seizures.

It is suggested that two factors influence the mental development of older phenylketonuric patients: (1) amount of permanent damage the central nervous system has suffered (occurring in first two or three years of life); and (2) the continuing presence of some neurotoxic agent(s).

Berlow, Stanley; Arends, Robert and Borsch, Roy: Problems in the Outpatient Management of Phenylketonuria. JOURNAL OF PEDIATRICS, 1962, 60, 140-141 (January).

The authors evaluate their experience with dietary treatment of 10 phenylketonuric patients ranging in age, at onset of therapy, from 14 months to 7 years, who have been on a dietary regimen for 2 to 5 years. They believe that management on an outpatient basis is practicable. They also believe that improvement can occur even if the diet is begun as late as 4 years of age and that gains can be made despite consistently elevated blood phenylalanine levels. They emphasize that factors other than diet contribute to the success or failure of treatment, one of the most important being the mother-child relationship. Effort should be directed to the psychiatric as well as the biochemical aspects of an individual child's problem.

Berman, Phyllis W.; Graham, Frances K.; Eichman, Peter L.; and Waisman, Harry A.: Psychologic and Neurologic Status of Diet-Treated Phenylketonuric Children and Their Siblings. PEDIATRICS, 1961, 28, 924-934 (December).

The neurologic status and intelligence of eight diet-treated phenylketonuric children were compared with that of 11 unaffected children and 3 untreated siblings. Although intelligence was significantly higher in treated than in untreated children, and this was especially marked in the children treated early, all treated children were significantly less intelligent than their unaffected siblings. The loss in intelligence probably cannot be ascribed to poor chemical control, as treated children maintained phenylalanine levels within the normal range throughout treatment, with occasional brief exceptions. Neurologic findings paralleled the results of intelligence testing. There were no suggestive or positive findings among the unaffected children. Children treated early had some relatively minor findings, while children treated late and those who were untreated had a higher percentage and more marked signs of neurologic defect.

Berry, Helen K.; Sutherland, Betty S.; Guest, George M.; and Umbarger, Barbara: Chemical and Clinical Observations During Treatment of Children with Phenylketonuria. PEDIATRICS, 1958, 21, 929-940 (June).

Three phenylketonuric children between the ages of $2\frac{1}{2}$ and $4\frac{1}{2}$ years were treated with 3 different diets low in phenylalanine over a period of 18 months. All 3 showed improvement in motor ability, lengthened attention span, and decrease in irritability. No change in mental status on objective testing was demonstrated. Symptoms, however, were so improved that parents were unwilling for children to go back to normal diets.

Bickel, Horst; Gerrard, John; and Hickmans, Evelyn M.: Influence of Phenylalanine Intake on Phenylketonuria. LANCET, 1953, 2, 812-813, (October 17).

A low phenylalanine diet produced beneficial effects in a child with phenylketonuria that seemed unequivocal although the degree of mental development finally attained remains to be seen after prolonged treatment. Special controlled trials of the diet were made with special attention to very young children.

Bickel, Horst; Gerrard, John; and Hickmans, Evelyn M.: The Influence of Phenylalanine Intake on the Chemistry and Behaviour of a Phenylketonuric Child. ACTA PAEDIATRICA, 1954, 43, 64-77 (January).

A two-year-old child with phenylketonuria was treated with a diet low in phenylalanine. Appreciable improvement in the child's mental status and a fall in the level of phenylalanine in blood and urine resulted. When phenylalanine was again given in fairly

large amount, there was an immediate, dramatic deterioration in the child's mental and biochemical condition.

Bickel, Horst; Boscott, Ronald J.; and Gerrard, John: Observations on the Biochemical Error in Phenylketonuria and Its Dietary Control. (Proceedings of the First International Neurochemical Symposium, held at Magdalen College, Oxford, July 13-17, 1954). [In] BIOCHEMISTRY OF THE DEVELOPING NERVOUS SYSTEM, edited by Heinrich Waelsch. New York, N.Y.: Academic Press, Inc., 1955. (pp. 417-430).

A phenylalanine-restricted diet has been given to 4 children with phenylketonuria for periods ranging from 3 months to 2½ years. So far this has produced improvement in the biochemical, physical, neurologic and mental status in varying degree in all patients. Results of biochemical studies are described. No definite relationship was found between severity of the mental condition and phenylalanine and tyrosine plasma levels, or urinary phenylalanine and phenylpyruvic acid excretion.

Bickel, H. and Grueter, W.: The Dietary Treatment of Phenylketonuria -- Experiences During the Past Nine Years. PROCEEDINGS OF THE FIRST INTERNATIONAL CONFERENCE ON MENTAL RETARDATION. New York-London: Grune & Stratton, 1960. pp. 272-276.

The authors review their experience with treatment of 11 phenylketonuric patients and compare their results with comparable findings drawn from reports on 79 cases treated by others. In 47 treated cases their data on mental development were compared with 19 untreated cases. Their findings showed that in the untreated group the development of intelligence continued to fall the first 10 to 14 years of life after which it remained more or less stationary. For those patients started on the diet between 1 and 5 years of age they found, as compared with untreated cases, an average IQ increase of 18 percent, while 9 cases put on the diet before 20 weeks of age developed normally. After age 5, treated patients showed little improvement, though there still was an average increase of nearly 6 percent by comparison with untreated cases. On the basis of these findings, the authors believe there is sufficient reason to continue the diet up to the age of 10 years. They stress the importance of starting the diet in early infancy, if possible.

Bickel, H. and Grüter, W.: Management of Phenylketonuria. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (pp. 136-172).

Factors involved in the preparation of a phenylalanine-restricted diet and the biochemical changes that take place as a result of dietary treatment are described. Available knowledge about the intellectual response of phenylketonuric patients to the diet is reviewed and the findings reported in the literature are summarized and analyzed with particular attention to age at which treatment was initiated. Other changes under the diet are summarized in general terms.

Blainey, J. D. and Gulliford, R.: Phenylalanine-Restricted Diets in the Treatment of Phenylketonuria. ARCHIVES OF DISEASE IN CHILDHOOD, 1956, 31, 452-466 (December).

Six cases of phenylketonuria have been treated with low-phenylalanine diets for periods up to four years. Detailed metabolic studies were conducted on two patients. Abnormal levels of increased phenylalanine in blood and urine and their abnormal products were completely corrected by limiting phenylalanine intake to 15 mg. per kg. per day.

High carbohydrate diets are essential in treatment of children on restricted phenylalanine intakes. The goal should be 110 calories per kg. per day of which 70 percent should be carbohydrate.

Changes in condition of patients, including mental status, behavior and locomotion, are discussed in relation to age and degree of dietary control.

Blainey, J. D. and Squire, J. R.: The Management and Diagnosis of Phenylketonuria. PROCEEDINGS OF THE LONDON CONFERENCE ON THE SCIENTIFIC STUDY OF MENTAL DEFICIENCY (1960). Dagenham, England: May & Baker Ltd., 1962. Vol. 1, pp. 119-125.

The authors present a concise review of some of the case-finding and research investigations carried out in England to support their conclusion that diagnosis at an early age followed by adequate and effective treatment will permit normal development in a high proportion of phenylketonuria cases.

Brimblecombe, F. S. W. and Stoneman, Margaret E. R.: The Treatment of Phenylketonuria. PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, 1958, 51, 1019 (December).

Three cases of treated phenylketonuria are presented which demonstrate how the effect of treatment may vary with the severity of the case and the age at which treatment is started.

Brimblecombe, F. S. W.; Stoneman, Margaret; and Maliphant, R.: Dietary Treatment of an Infant with Phenylketonuria. LANCET, 1959, 1, 609-611 (March 21).

This case report is of particular interest because the infant described had pyloric stenosis and also was found to have phenylketonuria. A diet low in phenylalanine begun at 17 weeks of age resulted in restoration and maintenance of normal intelligence. The importance of diagnosis of phenylketonuria in early infancy in order to prevent mental retardation is stressed.

Brimblecombe, F. S. W.; Blainey, J. D.; Stoneman, Margaret E. R.; Wood, B. S. B.: Dietary and Biochemical Control of Phenylketonuria. BRITISH MEDICAL JOURNAL, 1961, 5255, 793-798 (September 23).

Some practical observations about the management of phenylketonuric patients are presented from dietary aspect and that of chemical control. The requirements and purpose they serve in the construction of a low-phenylalanine diet are described, including phenylalanine, calorie requirements, requisites of phenylalanine-low protein hydrolysate, and calculation of additional calories and fat needed for normal weight gain and nutrition and also for maintaining effective biochemical control. An inadequate supply of calories, especially in carbohydrates, leads to negative nitrogen balance and elevation of phenylalanine levels.

Observations on two infants in whom difficulties arose from excessive restriction of phenylalanine are used to focus attention on the dangers of such restriction. In these infants, inadequate amounts of phenylalanine led to subnormal phenylalanine levels with loss of weight, vomiting, listlessness, and in one infant, severe eczematous rash which cleared rapidly on addition of more phenylalanine to diet. These investigators believe that infants under 12 months require a higher basic intake of phenylalanine than older children, possibly because of the rapid rate of growth of muscle at this age.

Centerwall, Willard R.; Centerwall, Siegfried A.; Acosta, Phyllis B.; and Chinnock, Robert F.: Phenylketonuria I. Dietary Management of Infants and Young Children. JOURNAL OF PEDIATRICS, 1961, 59, 93-101 (July).

Factors to be considered in selection of children with phenylketonuria for dietary treatment are discussed. It is suggested that a trial on the diet be given to all children under three years of age and selected patients over three with IQ's above 30.

Treatment of 10 infants and young children using low-phenylalanine formula, Lofenalac, has formed the basis of a simple plan of dietary management for children with phenylketonuria. The amounts of low-phenylalanine formula and the amounts and kinds of other foods that should be given are presented in tabular form. Some sample menus also are given. Hospitalization is not necessary or desirable in order to initiate diet. Frequent consultations with family providing opportunity for discussions and moral support by the physician are likely to be of great importance. The diet probably should be continued until the child is three years of age or older. These investigators expect to continue the diet at least in modified form into the school years.

Centerwall, Willard R.; Centerwall, Siegfried A.; Armon, Virginia; and Mann, Leslie B.: Phenylketonuria II. Results of Treatment of Infants and Young Children. A Report of 10 Cases. JOURNAL OF PEDIATRICS, 1961, 59, 102-118 (July).

Results of treatment of 10 infants and young children with phenylketonuria with a low-phenylalanine diet over a period ranging from 6 months to 3 years (average $22\frac{1}{2}$ months per child) are presented. The group includes 4 babies started on diet under 2 months of age, 1 at 8 months, and 4 from 1 to 3 years. Data include physical growth patterns, serum phenylalanine levels, EEG findings, personality and intelligence changes, and brief notes on individual diet control patterns. The 4 children who were placed on diet prior to age 2 months are developing within normal and low-normal range of intelligence. The 6 children started on diet from 8 months to 3 years have an average IQ of 72. Ten normal siblings have an average IQ of 103, and 5 untreated siblings with phenylketonuria have an average IQ of 24.

Chinque, Katherine M.: The Management of Children with Phenylketonuria. NURSING OUTLOOK, 1962, 10, 328-331 (May).

The author gives a running account of the daily activities (a normally routine schedule for almost all preschool children) and the behavior and responses of two phenylketonuric children as they occurred during the course of a few days. She then summarizes her observations in relation to the clinical manifestations of phenylketonuria, her evaluation of the behavioral patterns of children with this condition, and the parents' response to their phenylketonuric children.

Coates, Stephen: Results of Treatment in Phenylketonuria. BRITISH MEDICAL JOURNAL, 1961, 5228, 767-771 (March 18).

Psychological evaluations are presented for 31 cases of phenylketonuria that have been treated at the Hospital for Sick Children, Great Ormond Street, London. This research covered a 7-year period (1953-1960). The age of the children studied, at initiation of treatment, ranged from 4 weeks to 8 years, 9 months, 80 percent being under 3 years old. Of 28 cases in which the diet was given a fair trial, 22 showed improvement. In 12 instances this improvement was marked -- a rise in IQ of 9 or more points -- and appeared to be permanent. One patient born with average intelligence and treated since she was 4 weeks old has retained that level up to 5 years of age.

Dodge, Philip R.; Mancall, Elliott L.; Crawford, John D.; Knapp, John; and Paine, Richmond S.: Hypoglycemia Complicating Treatment of Phenylketonuria with a Phenylalanine-Deficient Diet -- Report of Two Cases. THE NEW ENGLAND JOURNAL OF MEDICINE, 1959, 260, 1104-1111 (May 28).

Two phenylketonuric children in whom hypoglycemia developed during the course of treatment with a phenylalanine-restricted diet are described.

Refusal to take an adequate amount of an unpalatable diet over a period of weeks or months resulted in a state of undernutrition accompanied by fatty changes in the liver. On this background, a short period of fasting resulted in severe hypoglycemia, with convulsions and coma.

Horner, Frederick A., and Streamer, Charles W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria; Clinical Observations in Three Cases. JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 1956, 161, 1628-1630 (August 25).

The authors report their clinical observations on three treated patients with phenylketonuria. Two preschool age children, treated for about 10 months, showed improvement in behavior and became psychologically testable. A newborn sibling of one of these children was followed from birth and placed on diet when the ferric chloride test became positive at 8 weeks of age. At time of writing, the infant showed normal motor and mental development, and no signs of abnormality had been detected.

Horner, F. A.; Streamer, C. W.; Clader, D. E.; Hassell, L. L.; Binkley, E. L., Jr.; and Dumars, K. W., Jr.: Effect of Phenylalanine-Restricted Diet in Phenylketonuria II. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1957, 93, 615-618 (June).

Six patients with phenylketonuria have been under treatment with phenylalanine-restricted diets for periods varying from 8 to 22 months. The two children who began dietary treatment at age five are showing sustained gains in intellectual functioning. Of the two children who began treatment at age three, one is showing marked acceleration in development while the second shows little change after 14 months on the diet. Two newborn infants treated are following a healthy developmental pattern after 21 and 7 months respectively. On the basis of these observations, the authors suggest that treatment of older phenylketonurics may prove valuable in some cases. The treatment of newborns may prevent the characteristic and profound mental changes associated with the disease.

Horner, Frederick A. and Streamer, Charles W.: Phenylketonuria Treated from Earliest Infancy; A Report of Three Cases. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1959, 97, 345-347 (March).

The developmental patterns of three phenylketonuric children treated from earliest infancy are reported. After $3\frac{1}{2}$ years, $2\frac{1}{4}$ years, and 1 year, respectively, the patterns of mental and motor activity are considered to be normal.

Horner, Frederick A.; Streamer, Charles W.; Alejandrino, Lourdes L.; Reed, Linda; and Ibbott, Frank: Termination of Dietary Treatment of Phenylketonuria. NEW ENGLAND JOURNAL OF MEDICINE, 1962, 266, 79-81 (January 11).

Observations on the effect of termination of phenylalanine-restricted diet at four years of age are reported on three children with phenylketonuria treated from earliest infancy. During the $2\frac{1}{2}$ years, $1\frac{1}{2}$ years, and 2 months, respectively, to the date of this report, no deterioration of their satisfactory mental development has been noted.

Hsia, David Y-Y.; Paine, Richmond S.; Knox, W. Eugene: Nutritional and Chemical Pitfalls in the Treatment of Phenylketonurics by Means of Low-Phenylalanine Diets. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1957, 94, 495-498 (November).

The authors report experience with 22 phenylketonuric patients, ranging from age 6 months to 60 years, who have been maintained on a low-phenylalanine diet for one year or longer. Findings indicate that long term treatment of phenylketonuria by means of a synthetic diet low in phenylalanine content can be achieved. In order to be carried out properly, it requires collaborative effort of a team trained in clinical medicine, biochemistry and nutrition.

Hsia, David Y-Y.; Knox, W. Eugene; Quinn, Karl V.; and Paine, Richmond S.: A One-Year Controlled Study of the Effect of Low-Phenylalanine Diet on Phenylketonuria. PEDIATRICS, 1958, 21, 178-202 (February).

Twenty-four patients with phenylketonuria from State institutions in Massachusetts were divided into 12 matched pairs, comparable as to age, sex, intelligence and length of institutional placement. One member of each pair was selected by lot to receive a phenylalanine deficient diet for a 12-month period, the other member of the pair receiving a control diet. At end of test period, patients were evaluated in terms of adequacy of chemical control, changes in intelligence, behavior, skin condition, hair color, seizures, and EEGs.

Tentative conclusion was that the metabolic disturbances associated with elevated concentration of phenylalanine in plasma, characteristic of phenylketonuria, interfere with normal cerebral development rather than with the function of a normally developed brain.

Hsia, David Yi-Yung; Rowley, William; and Raskin, Nathaniel J.: Clinical Management of Phenylketonuria. QUARTERLY BULLETIN, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, 1962, 36, 25-32 (Spring Quarter).

Data are presented on the clinical management of 12 phenylketonuric patients started on low-phenylalanine diet before age three. Information on patients includes genetic family data, weights and

heights while on treatment, laboratory findings, biochemical control, dietary problems, and psychological evaluations. In addition, patients were seen in their own homes and an evaluation is made of the social and economic factors that emerged from these visits.

Data on the relationship between intelligence and age of patient when treatment was started was pooled with comparable series reported by Knox (PEDIATRICS, 1960, 26, 1-11 (July)) and Coates (BRITISH MEDICAL JOURNAL, 1961, 5228, 767-771 (March)). Conclusion is reached that dietary treatment is beneficial in preventing the mental defect in phenylketonuria, with the effect being most marked in patients under age 6 months, and age being less important if treatment is started late. In the 3 series of data discussed, only 21 percent of cases were diagnosed under 6 months old, thus emphasizing need for early detection programs.

The authors conclude that except in States where government agencies are willing to underwrite the cost of the special diet, treatment of phenylketonuria places an impossible burden on the family with an average or low income.

Hudson, F. P.: The Problem of Phenylketonuria. THE PRACTITIONER, 1960, 184, 473-476 (April).

Hudson, F. P.: Phenylketonuria. BRITISH MEDICAL JOURNAL, 1961, 5232, 1105-1106 (April 15).

In these two articles, this pediatrician puts on record the results of his experience with treatment of 11 phenylketonuric children who have come under his care at Alder Hey Children's Hospital, Liverpool. He believes that the time has come to systematically collect information on all cases in whom treatment was started under age six months.

Hudson, F. P.; Dickinson, R. A.; and Ireland, J. T.: Experiences in the Detection and Treatment of Phenylketonuria. PEDIATRICS, 1963, 31, 47-57 (January).

Accumulated experience in the detection and treatment of phenylketonuria in a large children's hospital during the past 5 years is described. Of the 30 confirmed cases of phenylketonuria, 14 have received dietary treatment and their current status is presented. Early examination detected phenylketonuria in three siblings of known cases. One exceptional case showed an unusually low phenylalanine level and atypical results of tolerance tests, but routine urine tests were typical. Clinical investigation of this case is presented in detail. Results of laboratory investigations are delineated for each of six cases with false-positive ferric chloride tests. In an appendix, the investigators describe their paper chromatographic method for plasma phenylalanine determination.

Kirman, Brian H.: Phenylketonuria: Clinical Aspects. CEREBRAL PALSY BULLETIN, 1961, 3, 244-248 (June).

Clinical aspects of phenylketonuria are presented, including diagnosis, carriers course of the disease, life expectancy, and treatment. In this author's opinion, dietetic treatment is tedious and difficult. In view of lack of control, validation of results is still sub judice. Ideal treatment would be substitution of the missing enzyme. Short of this, work on different approaches to produce desired chemical changes in blood and urine has been progressing in the right direction.

Knox, W. Eugene: An Evaluation of the Treatment of Phenylketonuria with Diets Low in Phenylalanine. PEDIATRICS, 1960, 26, 1-11 (July).

All cases of phenylketonuria treated with a low-phenylalanine diet, reported and published up to December 1959 were reviewed and evaluated. Available information regarding untreated phenylketonuric cases was also investigated. The author concluded that a sufficient number of cases have been treated to assess the value of treatment when all published results are pooled and compared at different ages and with natural history of the disease in untreated patients.

Forty-four patients with phenylketonuria over three years of age who received treatment showed no impressive change in mental or neurologic status. Findings on 43 patients with phenylketonuria treated before age three were evaluated in detail. Twenty untreated cases with IQ above 60 were identified. The treated group had 18 times as many with an IQ above 60 and twice as many with a normal EEG as the untreated group. Over the three-year period studied, a minimal loss of nearly five points in IQ occurred each 10 weeks that treatment was delayed. The low-phenylalanine diet started in the early months of life is effective in preventing mental deficiency and neurologic abnormalities.

Lewis, Ian C.: An Unusual Case of Phenylketonuria. MEDICAL JOURNAL OF AUSTRALIA, 1960, 47 (2), 811-813 (November 19).

An infant, born into a family with an older phenylketonuric child, was diagnosed as having phenylketonuria within 18 days after birth and placed on a low-phenylalanine diet. At age $4\frac{1}{2}$ months his condition was so poor, death seemed imminent if the diet was continued, even though phenylalanine levels were satisfactory. Clinical examination revealed no known cause for the deterioration and the diet seemed to be the only source of difficulty. Treatment was abandoned and the child was put on a full-strength dried cow's milk preparation. His appetite improved, vomiting ceased, and he gained weight rapidly. Recovery was immediate and dramatic. A low-phenylalanine diet was resumed, this time gradually, taking about six weeks to return serum phenylalanine to a satisfactory level. The child seems to be thriving, and at 17 months, psychological testing placed his development within normal limits for his age.

Moncrieff, Alan and Wilkinson, R. H.: Further Experiences in the Treatment of Phenylketonuria. BRITISH MEDICAL JOURNAL, 1961, 5228, 763-767 (March 18).

The experiences of the past few years suggest that early detection of phenylketonuria and treatment of these very young infants offer a reasonable chance of preventing mental retardation. There are certain difficulties about early detection which should be overcome. More troublesome is the fact that the diet of the actively developing young baby may have to be more generous in phenylalanine, even to the extent of exceeding the normal blood level, if the child is to survive and thrive. Why some babies are more difficult than others is not yet clear. The dietetic control must be most closely followed by serial estimations of phenylalanine levels in the blood. Probably the simplest dietary treatment would be to use the available phenylalanine-free casein preparations but to add more milk than is usual (more than the maximum of three ounces daily allowed in older children). Whether or not more tyrosine and tryptophan should be given is not yet clear. There is need to learn more about the enzyme deficiency present, through experimental study. Whether dietetic restrictions can ever be relaxed is not known, although evidence on this is beginning to accumulate.

O'Daly, Seamus: Phenylketonuria Treated with a High Phenylalanine Intake and Casein-Hydrolysate/Aminoacid Mixtures. LANCET, 1961, 1, 1379-1383 (June 24).

In three low-grade phenylketonurics, administration of casein-hydrolysate/aminoacid mixture, with an adequate but not high protein intake, was accompanied by a small but significant decrease in serum phenylalanine levels. This finding might reflect an increased utilization of phenylalanine of a greater degree than would be explained by the expected increased protein anabolism. Arguments are presented in support of view that phenylketonurics having an amount of protein that would normally be considered adequate, either have a general protein depletion or a specific deficiency of phenylalanine, or perhaps both.

Royston, N. J. W. and Parry, T. E.: Megaloblastic Anaemia Complicating Dietary Treatment of Phenylketonuria in Infancy. ARCHIVES OF DISEASE IN CHILDHOOD, 1962, 37, 430-435 (August).

A detailed case report is presented of megaloblastic anaemia of infancy occurring during the dietary treatment of phenylketonuria. The anaemia is considered to be nutritional in origin. The case in point was a phenylketonuric infant who was started on a phenylalanine diet at age two weeks, suffered serious setbacks resulting in three hospital readmissions, and died at age 7 months.

Umbarger, Barbara: Phenylketonuria -- Treating the Disease and Feeding the Child. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1960, 100, 908-913 (December).

The author, who is a dietitian, comments on some of the problems which arise when the pediatrician prescribes a low-phenylalanine diet. She presents the experiences and observations made by the research team at the Children's Hospital Research Foundation, Cincinnati, Ohio, in relation to ten phenylketonuric children between the ages of 9 months and 7 years who were placed on low-phenylalanine diets. Problems that are discussed include (1) experience of hospitalization, (2) preparation and instruction of parents, (3) selection and acceptance of low-phenylalanine food supplement, and (4) planning of a long-range program. A major point is made that long-term dietary care requires the confidence and cooperation of the child and his parents working toward the goal of establishing normal attitudes toward food and toward the child's environment. There must be flexibility in carrying out the dietary program, allowing for individual differences and for adjustments to growth and change in the child's psychological and physical development.

Woolf, L. I.; Griffiths, Ruth; and Moncrieff, Alan: Treatment of Phenylketonuria with a Diet Low in Phenylalanine. BRITISH MEDICAL JOURNAL, 1955, 1, 57-64 (January 8).

An economically practicable diet low in phenylalanine has been devised. Three phenylketonurics (two idiots and one imbecile) have been fed this diet for $4\frac{1}{2}$ to 10 months. Their mental ages have been measured before and at intervals after starting the diet, their IQ's have risen, and they may reach educable levels. One child ceased having attacks of petit mal and his EEG became normal soon after starting the diet. The other child with petit mal developed major epilepsy and status epilepticus on the diet, but later improved. Otherwise normal physical health and growth were maintained. It is concluded that the mental deficiency in phenylketonuria is due to intoxication by phenylalanine or one of its metabolites and can be relieved by decreasing the dietary content of phenylalanine. The petit mal may also be due to this intoxication.

Woolf, L. I.; Griffiths, Ruth; Moncrieff, Alan; Coates, Stephen; and Dillistone F.: The Dietary Treatment of Phenylketonuria. ARCHIVES OF DISEASE IN CHILDHOOD, 1958, 33, 31-45 (February).

The results of treating 10 phenylketonurics with a diet low in phenylalanine are described. In almost every case there was a sharp and significant rise in IQ. An infant treated from the age of 5 weeks has remained at IQ 88 for nearly 2 years. The authors recommend that every infant's urine be tested with ferric chloride at age 21 days and treatment be started immediately if test reaction is positive.

The steps which led up to the development of a low-phenylalanine diet are described. Composition of the diet and its clinical effects are reviewed as well as the aesthetic and economic aspects. Phenylketonuria can be regarded as a problem in amino acid balance. Phenylalanine is an essential dietary component and if too little is fed, the infant becomes ill and may die. The daily requirement of dietary phenylalanine varies markedly from infant to infant and from time to time in the same infant during the first 18 months of life. Phenylalanine requirements for each infant must be determined individually and it is unsafe to attempt to treat an infant with a diet low in phenylalanine without biochemical control.

Allen, Richard J. and Gibson, Ralph M.: Phenylketonuria with Normal Intelligence. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1961, 102, 115-122 (July).

A 12-year-old boy with phenylketonuria and normal intelligence and a behavior disorder is presented. During the 2-year interval of clinical observation under psychological and EEG control, there was gradual behavioral improvement without any significant change in basic intelligence. A 7-month interval of dietary therapy also did not have any striking effects. The implications of normal intelligence in phenylketonuria in terms of etiology, inheritance, and the search for additional cases are discussed.

Bickel, H. and Grüter, W.: Management of Phenylketonuria. The Intellectual Response. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 145-167).

A detailed analysis and systematic summarization of information available in the literature is presented: (1) for cases where repeated mental or developmental testing was performed but no treatment was given, and (2) for cases where sufficient information was recorded to judge the state of development before and after treatment. Data are analyzed in relation to different age groups, and conclusions are reached regarding the relationship between age and the course of mental development in untreated and in treated patients with phenylketonuria.

Caudle, Harold V.: Phenylketonuria without Mental Retardation. PEDIATRICS, 1960, 26, 502 (September).

The author reports an untreated child with phenylketonuria and above-normal intelligence - a performance IQ of 134 at age 2 years, 9 months. Concentration of phenylalanine in serum is shown in table form along with corresponding psychometric test results (Merrill-Palmer Scale).

Coates, Stephen; Norman, A. P.; and Woolf, L. I.: Phenylketonuria with Normal Intelligence and Gowers' Muscular Dystrophy. ARCHIVES OF DISEASE IN CHILDHOOD, 1957, 32, 313-317 (August).

The case reported is that of a child with normal intelligence who has the extremely rare combination of phenylketonuria and Gowers' muscular dystrophy. No connection is established between the two diseases which seemed to be a chance occurrence in this particular patient.

Psychological tests showed the child to be of average intelligence with an IQ of 103 at age 6½. Clinical and biochemical findings and their implications in relation to phenylketonuria are discussed

in detail. Treatment for 3 months with a low phenylalanine diet did not cause any clinically detectable improvement in the muscular dystrophy. There was no significant change in intelligence, though this was not unexpected in so short a period of treatment. It did not seem justifiable to prolong dietary treatment in a child of this age and mental development.

In an addendum, it is noted that when the child was seen again, psychological test results showed that over a period of 2 years, his IQ had fallen by an average of 18 points. In view of this and his mother's feeling that he had been better while on a low-phenylalanine diet, this treatment was resumed.

Cowie, Valerie A.: An Atypical Case of Phenylketonuria. LANCET, 1951, 1, 272-273 (February 3).

The characteristics of this case of phenylketonuria differ from those usually described. In this case the normal neurological findings, the normal appearance, stance, and gait, the dark skin, hair, and eyes, and the relatively high mental level all seemed to belie the fact that the child was phenylketonuric. The chemical tests on his urine left no doubt, but it is of interest that his average daily excretion of phenylpyruvic acid was only half what is usual in phenylketonuric patients. The explanation of the normal physique and high mental grade may be that the biochemical error is incomplete or in some way compensated, and that a certain amount of phenylalanine can follow the normal pathway of metabolism. The patient's mental level appears to be higher than any previously recorded with phenylketonuria.

Cowie, Valerie and Brandon, M. W. Gillian: Follow-up Note on an Atypical Case of Phenylketonuria. JOURNAL OF MENTAL DEFICIENCY RESEARCH, 1958, 2, 55-58 (December).

An atypical case of phenylketonuria first reported by Cowie in 1951 (LANCET, 1951, 1, 272-273 (February 3)) has been followed up. Findings comparable to those previously made are presented. At age 16, the patient is within the limits of normal intelligence, shows none of the physical characteristics commonly associated with phenylketonuria, and his metabolic disturbance is mild. Biochemical findings indicate that although he is indisputably phenylketonuric, fasting serum phenylalanine levels obtained are well below the level usually found in phenylketonuria.

The suggestion is made that the study of heterozygotes would be of particular value in elucidating the relationship between various effects, biochemical, psychological and clinical, of the phenylketonuric gene.

Hsia, David Y. Y.; Knox, W. Eugene; and Paine, Richmond S.: A Case of Phenylketonuria with Borderline Intelligence. JOURNAL OF DISEASES OF CHILDREN, 1957, 94, 33-39 (July).

The case of a 13-year-old phenylketonuric girl with borderline to dull normal intelligence is reported. She has an 18-year-old institutionalized phenylketonuric sister whose I.Q. was most recently estimated at 4. The subject of the present report, who was discovered in the course of a survey for heterozygotes in relatives of known phenylketonurics, was in the sixth grade and scored an I.Q. of 78 by the Wechsler method and 69 by the Stanford-Binet. This case lends support to the existence of phenylketonurics with near-normal intelligence, of whom at least three have already been reported in the literature but less completely documented chemically and psychologically. The existence of cases in this intelligence range suggests the need for great caution in evaluating effects of diets low in phenylalanine or other experimental treatment of the disease.

Leonard, Stanley A., and McGuire, Frederick L.: Phenylketonuria: An Unusual Case. JOURNAL OF PEDIATRICS, 1959, 54, 210-214 (February).

A brief review of the literature on phenylketonuria is presented with special emphasis on the spectrum of mental retardation. An unusual case of phenylketonuria was found to be of borderline intelligence after evaluation chemically, physically, and psychologically. Serum phenylalanine levels did not correlate with the patient's I.Q.

Psychological evaluation found the patient high in ability for rote memory and gives hope that increased mental age may be obtained with continued environmental security. The patient was not treated with low-phenylalanine diet because of poor experimental results with use in older children, in addition to the fact that she is asymptomatic. Phenylpyruvic oligophrenia is no longer correct terminology for the syndrome of phenylketonuria.

Low, Niels L.; Armstrong, Marvin D.; and Carlisle, John W.: Phenylketonuria. Two Unusual Cases. LANCET, 1956, 2, 917-918 (November 3).

Two cases of phenylketonuria are reported in which the patients had greater mental ability than usual in this disease. Normal or near-normal intelligence in phenylketonuria could presumably exist under three conditions: (1) during the first few months of life, because the biochemical abnormalities, seizure disorder and deterioration are usually not yet present (Armstrong and Binkley); (2) in children who have been maintained on a restricted phenylalanine intake before deterioration becomes evident or very shortly after (Armstrong and Binkley; Horner and Streamer); and (3) in persons in whom the oxidation of phenylalanine is not completely blocked, as perhaps in the two present cases.

Partington, M. W.: Variations in Intelligence in Phenylketonuria.
CANADIAN MEDICAL ASSOCIATION JOURNAL, 1962, 86, 736-743 (April).

The distribution of intelligence is presented for 75 patients, age two years or older, with untreated phenylketonuria. The results were compared with comparable data collected by Knox (PEDIATRICS, 1960, 26, 1-11 (July)) and were found to be closely similar. In both series, over 90 percent of untreated patients had an IQ of 60 or less. Fasting plasma phenylalanine levels were measured in 51 patients and phenylalanine load tests were carried out in 34. No correlation was found between intelligence level and biochemical tests except that three patients with comparatively high intelligence (IQ over 60) had comparatively low fasting plasma phenylalanine levels (less than 25 mg. percent).

A patient with untreated phenylketonuria and normal intelligence (IQ 102) is reported. Her family and three children (two with phenylketonuria and one normal) are described.

Three families are presented to demonstrate that mental retardation in the sibling of a patient with phenylketonuria is not necessarily due to phenylketonuria.

Some observations on the effect of a low-phenylalanine diet on the intelligence of 12 patients with phenylketonuria are briefly described. Main beneficial effect of treatment appeared to be prevention of mental deterioration. All patients were less than two years old when first IQ assessment was made. The two children with the highest final intelligence had been started on diet at age of 10 days and 6 weeks, respectively. Until a greater number of patients have been treated with diet from this early age, full benefits of treatment will not be known.

Sutherland, Betty Steele; Berry, Helen K.; and Shirkey, Harry C.: A Syndrome of Phenylketonuria with Normal Intelligence and Behavior Disturbances. JOURNAL OF PEDIATRICS, 1960, 57, 521-525 (October).

Two patients with biochemical characteristics of phenylketonuria are described, one with normal and the other nearly normal mental ability. A phenylalanine restricted diet given one patient brought about alleviation of psycho-motor agitation, suggesting that dietary therapy in the older phenylketonuric child may be helpful. There appeared to be a definite relationship between IQ and serum phenylalanine concentration in these two children with essentially normal intelligence. The diagnosis of phenylketonuria in a child with normal mental ability may lead to recognition of families in which the abnormal gene might not otherwise be discovered.

Tapia, Fernando: Phenylpyruvic Oligophrenia. Report of a Case with Normal Intelligence. DISEASES OF THE NERVOUS SYSTEM, 1961, 22, 465-466 (August).

The author reports the case of a boy with normal intelligence who was first diagnosed as phenylketonuric at age eight when his four-year-old sister was found to have this condition. Psychological testing showed an IQ of 91. His behavior was characterized by nervousness, motor difficulties, and slight difficulty in speech, but he was considered to be making a satisfactory adjustment both at home and in school. After 6 months on a phenylalanine-restricted diet, some improvement in behavior was noted by parents and teacher, who reported sudden improvement in reading and especially in handwriting. Although such cases may be rare, the author points out that the possibility of this condition should be taken into account by pediatricians and child psychiatrists in cases of "nervousness" or "learning blocks."

Tischler, B.; Gibson, William C.; McGeer, E. G.; and Nuttall, J.: Degrees of Mental Retardation in Phenylketonuria. AMERICAN JOURNAL OF MENTAL DEFICIENCY, 1961, 65, 726-738 (May).

A correlation of the biochemical and psychological attributes of a known phenylketonuric and his two brothers is presented. The data show mental retardation to be marked in the first born, slight in the second and nil in the third. The two older boys are chemically phenylketonurics while the youngest shows no evidence of this metabolic block. All three children show similar abnormalities in the EEG but the youngest has the best regulated pattern of the three. The oldest child has been placed on a phenylalanine-restricted diet with some subsequent improvement in IQ, behavior and EEG. The second child is being followed in an attempt to assess any progression of the disease.

Acosta, Phyllis B. and Centerwall, Willard R.: Phenylketonuria: Dietary Management: Special Low-Phenylalanine Recipes. JOURNAL OF THE AMERICAN DIETETIC ASSOCIATION, 1960, 36, 206-211 (March).

Because phenylalanine is an essential amino acid, it must not be completely removed from the diet. The authors provide tables that give food values for calculating low-phenylalanine diets (including amount of phenylalanine in "equivalents"); exchange lists of Lofenalac, vegetables, fruits, breads, fats, desserts, free foods (little or no phenylalanine), foods to avoid (high phenylalanine content); and a few recipes for ice cream, puddings, and sauces. This is a practical article which provides useful information on diet in the care and management of children with phenylketonuria.

Lyman, Frank L. and Lyman, Julia K.: Dietary Management of Phenylketonuria with Lofenalac. ARCHIVES OF PEDIATRICS, 1960, 77, 212-220 (May).

Information is presented on diet for phenylketonuric patients using Lofenalac, a commercially prepared low-phenylalanine product, and "equivalents." The "equivalent," arbitrarily taken to equal 15 mg. of phenylalanine, was devised to make dietary calculations and exchanges simpler.

Tables show amount of calories, protein, and phenylalanine supplied by typical quantities of Lofenalac, and the amount of phenylalanine permitted in diets for children of various weights. Phenylalanine calculations are based on supplying approximately 11 mg. of phenylalanine per pound of body weight (25 mg. per kilogram) to provide for normal growth and development. The amount of phenylalanine in "equivalents" beyond that contained in Lofenalac also is listed. Another table shows phenylalanine content of approximate measures of various foods, including cereals, fruits, fruit juices, meats and eggs (for comparison), soups, and vegetables.

Lyman, Frank L.: Diets and Recipes. [In] PHENYLKETONURIA, edited by same. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p.173-250).

The author provides detailed and precise information on all aspects of the content of the low-phenylalanine diet used in the treatment of phenylketonuria. He includes an analysis of the composition of each of the commercially prepared low-phenylalanine foods; management of the diet specifically with Lofenalac; phenylalanine content of various foods; and about a fifty-page "cook book" of low-phenylalanine recipes.

THE LOW PHENYLALANINE DIET. Bureau of Public Health Nutrition,
California State Department of Public Health, Berkeley, California,
1963. 35 pp.

This description of the low-phenylalanine diet for phenylketonuria is intended for professional workers who may be giving guidance to parents of children with phenylketonuria. It provides some guide lines and tables on the basis of which the prescription and calculation of the low-phenylalanine diet can be based. The entire content of "PKU - A Diet Guide for Parents of Children with Phenylketonuria" with its suggestions for preparing the synthetic food product, daily meal guide, serving lists and recipes is included.

Brecher, Ruth and Brecher, Edward: The Conquest of the Body-Chemistry Diseases. FAMILY CIRCLE, 1959 (October). p. 21

This article describes briefly and in simple terms the biochemical causes and the hereditary nature of phenylketonuria and other biochemical diseases: diabetes, pernicious anemia, epilepsy, schizophrenia, atherosclerosis, muscular dystrophy, myasthenia gravis, and multiple sclerosis. It relates the case of a family in which there are two children with phenylketonuria - one who received dietary treatment and is normal, and the other who received no treatment and is mentally retarded. A list with addresses of the major private agencies concerned with these diseases is included.

Brecher, Ruth and Brecher, Edward: Saving Children from Mental Retardation. SATURDAY EVENING POST, 1959, (November 12). p. 32.

The authors present interestingly what is known today about the causes, diagnosis, treatment and prevention of mental retardation. The five major ways in which a child's brain development may be impaired are described. The article includes a discussion of phenylketonuria, galactosemia, "maple sugar disease," Rh disease, hydrocephalus, measles, rubella, and retardation caused by emotional deprivation. Significant research concerning causes of mental retardation is described.

Centerwall, Siegfried A., and Centerwall, Willard R.: AN INTRODUCTION TO THE CHILD WHO HAS PHENYLKETONURIA. Department of Pediatrics, College of Medical Evangelists, 1720 Brooklyn Avenue, Los Angeles 33, California. 1958. 7 pp., 20 cents.

The Centerwalls' have written a commendable booklet to help parents understand more about this condition which, while it is rare, is of particular concern as more is being learned about ways to prevent mental damage to the child who is born with this disorder.

PKU - A DIET GUIDE FOR PARENTS OF CHILDREN WITH PHENYLKETONURIA. Bureau of Public Health Nutrition, California State Department of Public Health, Berkeley, California, 1963. 19 pp.

This booklet is an excellent presentation of what phenylketonuria is and the diet program for its treatment written for parents with a phenylketonuric child. The first part defines the disease, its inheritance, diagnosis, symptoms, and management. The second part describes the low-phenylalanine diet and relates it to the problems of weaning, self-feeding, and the anxieties that all parents have with children on strict diets. A meal guide, serving lists of foods, and recipes for a low-phenylalanine diet are included.

Anderson, John A.; Gravem, Howard; Ertel, Robert; and Fisch, Robert: Identification of Heterozygotes with Phenylketonuria on Basis of Blood Tyrosine Responses. JOURNAL OF PEDIATRICS, 1962, 61, 603-609 (October).

Differences in responses of tyrosine concentration in serum to a two dose oral loading test with L-phenylalanine provided good separation of heterozygotes with phenylketonuria from control subjects. Determination of a discriminating factor by combination of either the fasting, one, and two hour tyrosine values, or only the one and two hour values, permitted separation of the two groups with approximately a 5 percent error. Discriminating values so derived gave an expression of differences in rate of formation of tyrosine from L-phenylalanine within the two hour period and appeared to be a critical method of measuring the presence of a partial gene-enzyme deficiency.

Anderson, John A.; Yarbrow, Marina; and Doeden, Doris: Hereditary Abnormality in Metabolism of Tryptophan in a Phenylketonuric Family. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1961, 102, 717-718 (November).

A disturbance in the metabolism of tryptophan resembling pyridoxine deficiency has been observed in a parent phenylketonuric heterozygote mother and in her three sisters, two of whom were also heterozygous for the phenylketonuric gene. Twelve of the 15 living children of 3 of the mothers have been studied for the presence of tryptophan metabolic abnormality. A metabolic limitation in the metabolism of tryptophan similar to that found in their mothers was observed in 5 of the 12 children.

Carter, C. O. and Woolf, L. I.: The Birthplaces of Parents and Grandparents of a Series of Patients with Phenylketonuria in South-east England. ANNALS OF HUMAN GENETICS, 1961, 25, 57-64 (May).

A comparison was made of birthplaces of parents and grandparents of a series of patients with phenylketonuria (38) with those of parents and grandparents of three control series of patients (303) with Hirschsprung's disease, congenital dislocation of the hip, and coeliac disease. The index patients in each series were restricted to those referred to The Hospital for Sick Children, between 1949 and 1959, from homes in south-east England.

Findings showed that a high proportion of the parents and grandparents of the phenylketonuric patients were born in Ireland and west Scotland. The frequencies, relative to the control patients, of phenylketonurics with grandparents born in Ireland or west Scotland, suggest that the frequency of the gene for phenylketonuria is about four times as high in the population of these parts of the British Isles as in the population of south-east England.

Centerwall, Willard R. and Neff, Charles A.: Phenylketonuria. A Case Report of Children of Jewish Ancestry. ARCHIVES OF PEDIATRICS, 1961, 78, 379-384 (October).

A family case history is presented in which two of three children have phenylketonuria and between them illustrate many of the frequently encountered features of this disease, which are described. Although phenylketonuria has been detected in all races and most nationalities throughout the world, it has been particularly rare in people of Negro or Jewish ancestry. The authors believe that this case history is the second reported instance in the world's medical literature in which one or both parents of phenylketonuric children are Jewish. This Jewish mother and her relatives are proud of their nationality background, and they believe they represent a pure Jewish stock. Yet the fair complexion, blond hair, and blue eyes of their young mother raise the possibility of some outside contamination of the Semitic line.

In an addendum the authors note that 10 cases of phenylketonuria among children were reported by a team of Israeli investigators. (Cohen, Bodonyi, and Szeinberg: Phenylketonuria in Jews. LANCET, 1961, 1, 344-345 (February 11).) These children were in "oriental" and "Yemenite" families of non-Ashkenazi Jewish heritage. Among patients of Ashkenazi Jewish heritage, there were no phenylketonurics found.

It is the Ashkenazi group who form the majority of Jews in Europe, England, and the United States and this probably accounts for the rarity of phenylketonuria among Jews examined in these countries. In the Centerwall and Neff report, it is probable that Ashkenazi heritage is mainly involved.

Cohen, Philip and Kozinn, Philip J.: Phenylpyruvic Oligophrenia in a Jewish Child. JOURNAL OF PEDIATRICS, 1949, 34, 76-79 (January).

In studies made thus far, it has been found that phenylketonuria occurs predominantly among Anglo-Saxon, Nordic, Irish and Italian stock. It rarely has been found in people of Negro or Jewish ancestry. This is the first case report of phenylketonuria in a Jewish child. The genetics and metabolic error of the disease are discussed briefly.

Cohen, Bernard E.; Bodonyi, Eva; and Szeinberg, Arie: Phenylketonuria in Jews (letter to editor). LANCET, 1961, 1, 344-345 (February 11).

Cohen, B. A.; Szeinberg, A.; Polak, S.; Boichis, H.; Bodonyi, E.; Hirshorn, N.; and Bar-or, R.: Phenylketonuria in Israel. JOURNAL OF THE ISRAEL MEDICAL ASSOCIATION, 1962, 63, 275-278 (October).

A survey of 1,000 children in institutions for mental defectives disclosed 10 phenylketonuric cases among Jewish families of non-Ashkenazi origin, including two families from Yemen, one each from

Iraq, Iran and Afghanistan. None were found among patients of Ashkenazi Jewish heritage. The total population of these institutions consisted of about 50 percent Ashkenazi and 50 percent non-Ashkenazi children. Thus phenylketonuria accounted for about 1.5 percent of non-Ashkenazi children in the mental institutions, a frequency comparable to that in England and the United States.

The inheritance pattern, clinical and biochemical picture of the affected children were identical with that described in other populations. However, none of the children have blue eyes or blond hair, an indication that defect of pigmentation is not a constant feature of the disease. The absence of Ashkenazim among the affected children found in this survey, taken in conjunction with the reported rarity of this disorder among Jews in Europe and the United States, predominantly of Ashkenazi origin, suggests differences in the incidence of this disease among the various Jewish communities. Whether the difference may be explained wholly by the rate of consanguineous marriages among oriental Jews or reflects differences in gene frequency remains to be investigated.

Cullen, A. M. and Knox, W. E.: O-hydroxyphenylacetic Acid Excretion in the Phenylalanine Tolerance Test for Carriers of Phenylketonuria. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1958, 99, 219-222 (October).

O-hydroxyphenylacetic acid (o-HPA) is an abnormal urinary metabolite of phenylalanine found in phenylketonuria and after phenylalanine dosage in heterozygotes of phenylketonuria. In patients with this disorder, the excretion of o-HPA is proportional to the blood phenylalanine level. Research undertaken by these investigators demonstrates that it is also formed by normal individuals with comparably elevated phenylalanine blood levels and, therefore, o-HPA formation is not dependent upon the presence of the phenylketonuric gene. It must be formed by enzyme systems other than the one disturbed in phenylketonuria.

Fujiki, Norio; Drew, Arthur L.; Miyake, Munetaka; Nemoto, Hiroki; Sujaku, Chokudo; and Shimada, Tsunehiro: A Case of Phenylketonuria in the Eta Resulting from the Mating of a Homozygous Father and a Heterozygous Mother. AMERICAN JOURNAL OF HUMAN GENETICS, 1961, 13, 64-68 (March).

The mating of a homozygous phenylketonuric with a heterozygous carrier of the phenylketonuric gene with the subsequent production of a homozygous phenylketonuric is reported. The case in point, an 18-year-old girl, was first seen by the investigators in an institution for the mentally retarded. Both parents were reported to be mentally deficient. Twenty-five members of the immediate family were examined in the process of tracing the lineage of the subject. The results of various biochemical studies made on certain members of the family are reported, including determinations for phenylpyruvic acid, fasting serum levels of phenylalanine, and phenylalanine tolerance tests.

The investigators believe that consanguinity may be presumed in this case because the family belongs to the "Eta Buraku," a social group which, for centuries, has been isolated from the remainder of the population.

Hsia, David Y.-Y. and Driscoll, Kathleen W.: Detection of Heterozygous Carriers of Phenylketonuria. LANCET, 1956, 2, 1337-1338 (December 29).

The authors describe observations made of heterozygous carriers of phenylketonuria without the use of a phenylalanine load. Plasma levels of phenylalanine were determined after an overnight fast in 37 parents of phenylketonurics and 34 normal adult controls. The plasma phenylalanine levels of the two groups overlapped considerably, but the difference between the means was significant.

The data presented add confirmatory evidence for the detection of heterozygous carriers of phenylketonuria, and suggest that the phenylalanine load merely brings out the difference between the two groups more strikingly.

Hsia, David Yi-Yung and Paine, Richmond S.: Phenylketonuria: Detection of the Heterozygous Carrier. JOURNAL OF MENTAL DEFICIENCY RESEARCH, 1957, 1, 53-65 (July).

Experimental work on the detection of the heterozygous carrier for phenylketonuria is reviewed with a detailed discussion of phenylalanine tolerance tests and fasting plasma phenylalanine levels, which have proven to be effective means of differentiating parents of known phenylketonurics from normal controls. Other possible approaches for the detection of carriers are discussed.

Hsia, David Yi-Yung and Steinberg, Arthur G.: Studies on Linkage between Phenylketonuria and the Blood Groups. AMERICAN JOURNAL OF HUMAN GENETICS, 1960, 12, 277-286 (September).

The authors report on linkage relationships between the genes for phenylketonuria and those for the blood groups. The data have been subjected to sequential analysis with the phenylketonuric gene being treated both as a recessive and as an intermediate dominant, where the heterozygote is identified by means of the phenylalanine tolerance test. Specifically, linkage between phenylketonuria and the ABO, MNS, Rh, P, K, and Fy loci was examined by Morton's sequential method, treating phenylketonuria as an intermediate dominant and recessive.

Linkage with ABO, Rh, or MNS as close as .1 or less is excluded. Linkage with K of .05 or less is excluded. The data were insufficient to permit other conclusions.

Hsia, D. Yi-Yung; Rowley, W. A.; and Huang, Irene: The Excretion of 5-Hydroxyindoleacetic Acid in the Heterozygous Carrier for Phenylketonuria. JOURNAL OF MENTAL DEFICIENCY RESEARCH, 1961, 5, 4-9 (June).

This study shows that the urinary excretion of 5-hydroxyindoleacetic acid is lower in a group of heterozygotes for phenylketonuria as compared with a group of normal controls following ingestion of a phenylalanine load. The depression in the synthesis of the 5-hydroxyindole compounds could well be due to the inhibition of 5-hydroxytryptophane decarboxylase by the increased levels of phenylalanine and its derivatives among the heterozygotes.

Jervis, George A.: Genetics of Phenylpyruvic Oligophrenia. JOURNAL OF MENTAL SCIENCE, 1939, 85, 719-762 (July).

The paper presents a genetic study of 200 cases of phenylpyruvic oligophrenia. Environmental and hereditary factors are discussed. In conclusion, the data are consistent with the quantitative requirements of the theory of monomeric recessivity, since (a) the ratio of affected to normal sibs in families with normal parents, when corrected by specific method of statistical analysis, is found to be 25 percent; (b) the rate of consanguinity among the parents of affected individuals is significantly higher than normal; (c) the distribution of the character among ascendant and collateral relatives follows the rules of monomeric recessivity. Phenylpyruvic oligophrenia, therefore, appears to be a clear illustration of a type of mental deficiency determined by a single autosomal recessive gene.

Jervis, George A.: Detection of Heterozygotes for Phenylketonuria. CLINICA CHIMICA ACTA, 1960, 5, 471-476 (July).

A method is described which can be used to detect the heterozygote for phenylketonuria. It is based on the determination of blood tyrosine at various intervals following the ingestion of a large dose of L-phenylalanine. The tyrosine curve in the carrier is intermediate between the flat curve of the phenylketonuric and the steep curve of the normal individual.

The author believes that the method based on tyrosine levels is preferable to the method based on phenylalanine levels because the differences in the former between normal and carrier are clear cut and no overlapping occurs.

Kang, Ellen and Paine, Richmond S.: Elevation of Plasma Phenylalanine Levels During Pregnancies of Women Heterozygous for Phenylketonuria. JOURNAL OF PEDIATRICS, 1963, 63, 283-289 (August).

Plasma phenylalanine levels were studied serially during the pregnancies of nine heterozygous mothers of previous known phenylketonuric infants. Pregnant heterozygous carriers of this disease

showed higher mean levels of phenylalanine in blood throughout pregnancy than did normal pregnant controls or non-pregnant heterozygotes.

The status of the new infant as to phenylketonuria or normality could not be predicted from graphs of maternal phenylalanine levels during pregnancy or from levels in cord blood. The phenylalanine concentration in the infant's serum 5 to 7 days after birth is a better indicator of the status of the newborn.

King, F. J. and Bowman, Barbara H.: Phenylketonuria: Five Affected Members in One Sibship. JOURNAL OF HEREDITY, 1960, 51, 86-90 (March-April).

A sibship is described in which 5 of 11 siblings are phenylketonuric. Investigation of the family's pedigree revealed that the parents of these children had a common great-great-grandfather. IQ scores of the parents, affected siblings, and non-affected siblings who could be contacted are given. Biochemical test results are presented.

Knox, W. Eugene: Incidence and Inheritance. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 11-51).

Available information about the occurrence of phenylketonuria and estimates of its incidence is reviewed, with careful cognizance of the influence of its original selective nature. This is followed by a description of the pattern of inheritance, and the characteristics of heterozygous carriers and tests for identification of this group. The author attempts to demonstrate possible interconnections of the gene and the enzyme involved in this disorder with the clinical symptoms which are used as markers for the gene.

Penrose, L. S.: Inheritance of Phenylpyruvic Amentia. LANCET, 1935, 2, 192-194 (July 27).

This is one of the early papers describing the familial character of the disease. When it was found that approximately one-fourth of the children in the involved families were affected, it was concluded that this was a simple autosomal recessive gene type of inheritance.

Penrose, L. S.: A Search for Linkage between the A, B, O Agglutinogens and Phenylketonuria. AMERICAN JOURNAL OF MENTAL DEFICIENCY, 1945, 50, 4-7 (July).

An investigation of the relationship between phenylketonuria and the blood agglutinogens A, B, O and A₁ gave a strong suggestion of the presence of genetic linkage. One of the families studied in the course of the survey included a diabetic case.

Penrose, L. S.: Phenylketonuria. A Problem in Eugenics. LANCET, 1946, 1, 949-953 (June 29).

The author discusses phenylketonuria with respect to the clinical picture, chemistry, heredity, detection of carriers, and eugenic prognosis. He concludes that for practical purposes we are still unable to identify carriers.

Penrose, Lionel S.: Rare Recessive Defects. In BIOLOGY OF MENTAL DEFECTS. Grune and Stratton, 1949. pp. 140-148.

The author discusses general principles relating to recessive defects and analyzes the evidence concerning the biological nature and causation of phenylketonuria.

Penrose, L. S.: Measurement of Pleiotropic Effects in Phenylketonuria. ANNALS OF EUGENICS, 1951, 16, 134-141 (September).

Measurements of the effects of the homozygous phenylketonuric gene are expressed in terms of the difference between means in normals and abnormals divided by the mean standard deviation. This index, D/S reaches a maximum of 16 for the concentration of phenylalanine in the cerebro-spinal fluid; for intelligence level, its value is nearly 6; and for hair color, approximately unity. Several other genetical traits are examined in a similar way. Doubt is thrown on the value of any attempt to separate major and minor genes since each gene can be shown to have both major and minor effects.

Penrose, L. S.: Data for the Study of Linkage in Man. Phenylketonuria and the ABO and MN Loci. ANNALS OF EUGENICS, 1951, 16, 241-243 (December).

Data are given on 14 families selected by the presence of at least one case of phenylketonuria. Analysis of this material, taken together with previously published data, leads to inconclusive results when searching for linkage of phenylketonuria with ABO. There was no indication of linkage with MN.

Renwick, J. H.; Lawler, Sylvia D.; and Cowie, Valerie A.: Phenylketonuria: A Linkage Study Using Phenylalanine Tolerance Tests. AMERICAN JOURNAL OF HUMAN GENETICS, 1960, 12, 287-322 (September).

The phenylalanine tolerance test as a means of detecting carriers of the phenylketonuric gene has been shown to be improved by correcting for the dose given. The four hour plasma sample is better than the fasting sample or the one or two hour samples for this discrimination which apparently is not improved by estimating the plasma tyrosine level concurrently.

The four hour test has been used in tracing the gene through three generations of several families as part of a linkage study. Data

relating to the ABO and phenylketonuria pair of loci are similar to those of other investigators in deviating in the direction of linkage, but even when all available data (from 74 informative families) are combined, the evidence for linkage is weak.

Salam, Maria: Phenylketonuria in a Child from the Middle East. AMERICAN JOURNAL OF DISEASES OF CHILDREN, 1963, 105, 102-103 (January).

The author reports an Armenian child found to have phenylketonuria during routine screening of children with mental defects or other neurological abnormalities in the Pediatric Neurology Clinic, American University Hospital, Beirut, Lebanon. Only 202 children were tested routinely before this child was found. Subsequently, three additional cases were detected among 60 inmates of an institution for retarded children, 2 Arab and 1 Armenian child.

This raises the possibility that the absence of reported cases of phenylketonuria from the indigenous population of the Middle East may be due to the lack of suitable screening programs rather than to a major difference in the geographical incidence of this disease.

Stadler, H. I.; Meyer, Hans; and Leland, Henry: Phenylpyruvic Oligophrenia in a Mulatto. JOURNAL OF NERVOUS AND MENTAL DISEASE, 1956, 124, 205-207 (August).

The authors report the case of a mulatto with a positive urinary test for phenylpyruvic acid and with mental deficiency. Laboratory and psychological findings are presented briefly. A picture of the youth (26 years old) strikingly demonstrates the blond hair and blue eyes commonly observed in the phenylketonuric patient. The authors believe their case strongly suggests the probable genetic linkage (pleiotropic effect) between albinism and phenylketonuria.

The point is made that there is very little information in the literature on phenylketonuria involving a member of the colored race. Reference is made to one case reported by J. Ferriera-Fernandes: Phenylpyruvic oligophrenia in melanoderma. BRASIL-MEDICO, 1960, 64, 225 (Stadler, et al.) state that, unfortunately, Fernandes does not describe the physical characteristics of his patient. Nordic constitutional qualities are hence not known. Fernandes expressed the feeling that the "abnormal occurrence of excretion of phenylpyruvic acid is indicative of a broader incidence among other races."

Tanaka, Katsumi; Matsunaga, E.; Handa, Yoshitoshi; Murata, Toshiro; and Takehara, Kazuo: Phenylketonuria in Japan. JAPANESE JOURNAL OF HUMAN GENETICS, 1961, 6, 65-77 (October).

Of 5,419 mentally defective persons in institutions examined by the ferric chloride test, 9 were found to be phenylketonurics, the frequency being 0.166 percent. Incidence of this abnormality in the general population was estimated as 16 to 18 per million.

Data of 22 sibships of phenylketonuria obtained by other investigators were analyzed. Of the 28 cases in these families, 27 are feeble-minded of various grades; one, a 15-month-old baby, was reported to be normal. The majority of patients (24 of the 28) have unusually fair skin, and all but 2 showed much reduced hair pigmentation. Except for one family in which the father and his only child were both affected, all the patients were born of normal parents between whom consanguineous marriages were frequent.

Wang, Hwa L.; Morton, N. E.; and Waisman, Harry A.: Increased Reliability for the Determination of the Carrier State in Phenylketonuria. AMERICAN JOURNAL OF HUMAN GENETICS, 1961, 13, 255-261 (June).

Heterozygous phenylketonuria carriers can be distinguished from homozygous normals with classification error occurring in less than 4 percent of the cases. The discriminant measure uses the weighted logarithms of fasting plasma phenylalanine level and levels at 1.5, 2 and 3 hours after administration of phenylalanine. For the best single measure the classification error is at least 9 percent. Use of levels at 1 and 4 hours does not increase the discriminating power of the measure, nor does tyrosine determination.

Woolf, L. I.; Ounsted, Christopher; Lee, Douglas; Humphrey, Michael; Cheshire, Neil M.; and Steed, G. R.: Atypical Phenylketonuria in Sisters with Normal Offspring. LANCET, 1961, 2, 464-465 (August 26).

Two phenylketonuric sisters appeared to have an unusual variant of the disease, with minimal damage to the central nervous system. Phenylpyruvic acid in the urine of one of them could be detected only by means of paper chromatography. No phenylalanine hydroxylase activity could be detected in either sister. None of their six children is mentally defective despite exposure to a phenylketonuric environment while in utero.

Armstrong, Marvin D. and Robinson, Kathryn S.: On the Excretion of Indole Derivatives in Phenylketonuria. ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, 1954, 52, 287-288 (September).

Patients with phenylketonuria excrete abnormal indole derivatives as well as the recently reported phenolic compounds and the previously known metabolites which are derived from phenylalanine. The indole derivatives have been observed in all of 15 patients studied. The occurrence of abnormal phenolic and indole metabolites indicates that the derangement of metabolism in phenylketonuria involves tyrosine and tryptophan as well as phenylalanine, and thus is more extensive than was previously supposed. Indolacetic acid has been identified as the indole derivative present in greatest amount in phenylketonuric urine.

Armstrong, Marvin D.; Shaw, K. N. F.; and Robinson, Kathryn S.: Studies on Phenylketonuria. II. The Excretion of O-hydroxyphenylacetic Acid in Phenylketonuria. JOURNAL OF BIOLOGICAL CHEMISTRY, 1955, 213, 797-804 (April).

O-hydroxyphenylacetic acid is a constituent of the urine of patients with phenylketonuria. The amount excreted ranges from 100 to 400 mg. per gm. of creatinine and is directly related to the phenylalanine levels in the blood. Normal persons also excrete o-hydroxyphenylacetic acid but at a level of less than 1 mg. per gm. of creatinine. It is probable that excretion of increased amount of this metabolite is not related in any direct way to the occurrence of the mental defect.

Armstrong, Marvin D.; Shaw, K. N. F.; and Robinson, Kathryn S.: Studies on Phenylketonuria. III. The Metabolism of O-tyrosine. JOURNAL OF BIOLOGICAL CHEMISTRY, 1955, 213, 805-811 (April).

The metabolism of DL-o-tyrosine has been studied in both normal and phenylketonuric individuals. There appears to be no abnormality in the manner in which o-tyrosine is metabolized in phenylketonuria. The possible origin and metabolism of o-tyrosine, the probable precursor of o-hydroxyphenylacetic acid, are discussed.

Armstrong, Marvin D., and Binkley, Edward L., Jr.: Studies on Phenylketonuria. V. Observations on a Newborn Infant with Phenylketonuria. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1956, 93, 418-420 (December).

From studies on a newborn infant with phenylketonuria, these investigators found that the phenylalanine level in the cord blood at birth is normal. Within a day or two after birth, however, as the infant began to take milk, the serum phenylalanine level rose. Phenylpyruvic acid appeared in the urine at 34 days of age. The highest concentration of phenylalanine in the blood was 62 mg./100 ml. at 24 days of age.

Armstrong, Marvin D., and Low, Niels L.: Phenylketonuria. VIII. Relation between Age, Serum Phenylalanine Level, and Phenylpyruvic Acid Excretion. PROCEEDINGS OF SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1957, 94, 142-146 (January).

The excretion of phenylpyruvic acid by patients with phenylketonuria is roughly proportional to their fasting serum phenylalanine levels. Phenylpyruvic acid is not detectable in urine of patients with serum levels below 15 mg. percent phenylalanine. Children less than 3 years old frequently show much higher serum levels of phenylalanine than older patients. The incidence of known phenylketonuria in Utah during the last 10 years has been 1 in 20,400 births.

Armstrong, Marvin D.; Centerwall, Willard R.; Horner, Frederick A.; Low, Niels L.; and Weil, William B., Jr.: The Development of Biochemical Abnormalities in Phenylketonuric Infants. CHEMICAL PATHOLOGY OF THE NERVOUS SYSTEM. (Proceedings of the Third International Neurochemical Symposium - Strasbourg, 1958.) New York, N.Y.: Pergamon Press, 1961. pp. 38-50.

This study was undertaken to observe the development of biochemical abnormalities in newborn infants with phenylketonuria in order to learn whether there are differences in the time of their development and what factors might be identified as influencing the rapidity of their development.

Three infants who were bottle fed developed high phenylalanine levels more rapidly than three who were breast fed, indicating that amount or type of protein food might be an important factor influencing rapidity of development of high blood levels of phenylalanine and the formation of abnormal metabolites. The suggestion is made that newborn siblings of known phenylketonurics might be kept on a low-protein diet until serum phenylalanine determination can be made for diagnosis.

Study findings support the hypothesis that there are marked differences between individuals in time of development of different biochemical abnormalities in phenylketonuria. Difference in time of appearance of phenylpyruvic acid may be especially significant since there has been some indication that patients with atypical high mental ability may excrete less phenylpyruvic acid than usual. If this acid is directly connected with damage to the nervous system which happens to phenylketonuric infants, production of large amounts of this acid by some infants at about one week of age but not until five weeks or later by others, may result in a great difference in the damage suffered in each case. Difference in timing of development of biochemical abnormalities rather than extent of the abnormality finally established may lead to great differences in neurologic damage and explain the lack of correlation between mental ability and biochemical abnormality as observed with older children.

Armstrong, Marvin D.: Biochemistry. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 62-95).

The author of this chapter has invested a great deal of his own highly productive research into the biochemical study of phenylketonuria. He puts into manageable form a myriad amount of knowledge available about the inherited biochemical defect, the metabolism of phenylalanine in phenylketonuria, and the development of biochemical abnormalities in phenylketonuric infants.

Baldrige, Robert C.; Borofsky, Leatrice; Baird, Henry III; Reichle, Frederick; Bullock, Donna: Relationship of Serum Phenylalanine Levels and Ability of Phenylketonurics to Hydroxylate Tryptophan. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1959, 100, 529-531 (March).

Following reduction of serum phenylalanine levels by use of low-phenylalanine diet, four phenylketonuric children under experimental study excreted increased amounts of 5-hydroxyindolacetic acid (5-HIAA). The ratio of urinary 5-HIAA to creatinine was about 5-fold greater for young phenylketonuric children, fed a low-phenylalanine diet for 4-10 months, than for untreated phenylketonurics. Oral administration of L-tryptophan to untreated phenylketonurics was followed by increase in 5-HIAA excretion. Following oral administration of 5-hydroxytryptophan, 10-15 percent was excreted as urinary 5-HIAA by an otherwise untreated phenylketonuric.

Berends, Heinz; Anderson, J. A.; Ziegler, M. R.; and Ruttenberg, Diane: Disturbance in Tryptophane Metabolism in Phenylketonuria. A.M.A. JOURNAL OF DISEASES OF CHILDREN, 1958, 96, 430 (October).

Measurements were made on the urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) to reflect changes in the metabolism of tryptophane. Study subjects were phenylketonuric children on normal diets and during administration of low-phenylalanine diets. Loading studies also were done on these children using L-tryptophan, L-phenylalanine, and during and following infusion with 5-hydroxytryptophan.

Preliminary findings are reported. There appears to be a competitive inhibition by high levels of phenylalanine for the tryptophan hydroxylase enzyme. The decarboxylation of 5-hydroxytryptophan to serotonin and oxidative deamination to 5-HIAA seems to proceed normally as indicated by an increase in 5-HIAA excretion following 5-hydroxytryptophan infusion.

Block, Richard J.; Jervis, George A.; Bolling, Diana; and Webb, Merrill: Chemical and Metabolic Studies on Phenylalanine. III. The Amino Acid Content of Tissue Proteins of Normal and Phenylpyruvic Oligophrenia Individuals. A Note on the Estimation of Phenylalanine. JOURNAL OF BIOLOGICAL CHEMISTRY, 1940, 134, 567-572 (July).

No significant differences were found in the amino acid composition of the proteins of the blood and tissues of normal and of phenylketonuric persons.

Borek, Ernest; Brecher, Arthur; Jervis, George A.; and Waelsch, Heinrich: Oligophrenia Phenylpyruvia. II. Constancy of the Metabolic Error. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1950, 75, 86-89 (October).

The serum level of free phenylalanine and phenyllactic acid was determined in 18 phenylketonuric patients. No correlation was found to exist between the degree of mental deficiency and the concentration of phenylalanine in serum. Phenylalanine concentration in the spinal fluid varied from 6.1 to 8.2 mg./100 ml. Authors postulate that although increased amount of phenylalanine is caused by metabolic error, its blood plasma level is determined by the ability of the kidney tubules to reabsorb the amino acid.

Bowman, Barbara H. and King, F. J.: Effects of Glutamine and Asparagine Supplements in the Dietary Regimen of Three Phenylketonuric Patients. NATURE, 1961, 190, 417-418 (April 29).

The objective of this research was to decrease the phenylpyruvic acid-phenylalanine ratio in phenylketonuric subjects through transamination by increasing the concentration of available amino donor, and to study the effects of this in selected patients over a period of several months. The results contribute evidence to the hypothesis that in phenylketonuria, phenylalanine is converted to phenylpyruvic acid by means of a transamination process which may be reversed by increasing the available amino donor. Reduction of the phenylpyruvic acid-phenylalanine ratio was accompanied by a slight but significant improvement in each subject's mental ability. No increase in IQ score was seen in the two subjects who showed no reduction in the phenylpyruvic acid-phenylalanine ratio. The direct cause of the increase in IQ scores in the two phenylketonuric subjects is unknown, although the decrease of toxic products formed from phenylpyruvic acid and its derivatives may be one possible influence.

Clegg, Marguerite Davis and Schroeder, W. A.: A Chromatographic Study of the the Minor Components of Normal Adult Human Hemoglobin, Including a Comparison of Hemoglobin from Normal and Phenylketonuric Individuals. JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 1959, 81, 6065-6069 (November 20).

An improved procedure is described for the separation of minor hemoglobin components in hemolysates of red blood cells, and hence for

purification of the main component. Comparison of the minor components of hemoglobin from normal and phenylketonuric individuals has failed to reveal any significant differences in the number or amounts. Thus, the abnormal amounts of free phenylalanine in the organism failed to influence the biosynthesis of the hemoglobin significantly.

Crome, L.; Tymms, V.; Woolf, L. I.: A Chemical Investigation of the Defects of Myelination in Phenylketonuria. JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY, 1962, 25, 143-148 (May).

Chemical analysis of the white matter of the brain in phenylketonuria is compared with that of age-matched controls. The total solids content is reduced in phenylketonuria and the percentage of the solids represented by cerebrosides and cholesterol is less than in normal individuals of the same age. Cholesterol esters were not found except in parts of the brain of one patient with leucodystrophy.

The findings are discussed in relation to the clinical and biochemical features of phenylketonuria. The laying down of myelin appears to be hindered in this disorder, but gradual active demyelination cannot be excluded.

Crome, L.: The Association of Phenylketonuria with Leucodystrophy. JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY, 1962, 25, 149-153 (May).

Schilder's disease (leucodystrophy) was found in a phenylketonuric. Three previous reports appear in the literature. Chemical analysis showed cholesterol esters to be present in the white matter and the content of cerebrosides and free cholesterol to be markedly reduced.

Dancis, Joseph and Balis, M. Earl: A Possible Mechanism for Disturbance in Tyrosine Metabolism in Phenylpyruvic Oligophrenia. PEDIATRICS, 1955, 15, 63-66 (January).

In vitro, L-phenylalanine partially inhibits the action of tyrosinase in tyrosine. The amount of inhibition is directly related to the concentration of L-phenylalanine. In the same concentration, D-phenylalanine produces no significant effect on the tyrosine-tyrosinase system. Parallel experiments with DL-alanine also indicate a specific effect by L-phenylalanine. It is suggested that because of the similarity in structure, L-phenylalanine competes with tyrosine for the enzyme tyrosinase.

Grüner, Hanns-Dieter; Koblet, Hans; and Woodard, Carol: Phenylalanine Metabolism in the Phenylpyruvic Condition. I. Distribution, Pool Size, and Turnover Rate in Human Phenylketonuria. JOURNAL OF CLINICAL INVESTIGATION, 1961, 40, 1758-1765 (September).

Four patients with phenylketonuria were subjected to studies of distribution, pool size, and turnover rate of free phenylalanine. Data were obtained from the disappearance curves of intravenously injected L-phenylalanine-C¹⁴. Experiments indicate no substantial intracellular

concentration, as derived by comparing the phenylalanine space to antipyrine space. A positive correlation existed between the free phenylalanine pool and its turnover time and of phenylalanine pool to plasma phenylalanine concentration.

Grüner, Hanns-Dieter; Koblet, Hans; and Woodard, Carol: Phenylalanine Metabolism in the Phenylpyruvic Condition. II. An Attempt to Calculate the Daily Incorporation of Phenylalanine into Proteins. JOURNAL OF CLINICAL INVESTIGATION, 1962, 41, 61-66 (January).

The rate of total body protein synthesis in three phenylketonuric patients was calculated from the disappearance of free phenylalanine- C^{14} from deproteinized plasma. Judging from this experiment, the authors believe that protein synthesis in phenylketonuric subjects is of the same order of magnitude as in non-phenylketonuric individuals, and that the values they obtained reflect the upper limit of daily protein synthesis in man.

Hsia, David Yi-Yung and Huang, Irene: The Metabolism of Indole-Compounds in Phenylketonuria. CEREBRAL PALSY BULLETIN, 1961, 3, 237-243 (June).

The cause of the mental defect in phenylketonuria is as yet unknown. Despite extensive studies both in vivo and in vitro there still is no clear evidence that any of the phenolic derivatives of phenylalanine, or phenylalanine in itself, acts as a "toxic" substance on the brain.

In another approach to the problem, the authors work toward defining the role of the indole compounds in the mental defect of phenylketonurics. Observations are presented regarding the levels of 5-hydroxy tryptamine, 5-hydroxy indoleacetic acid, and 5-hydroxy tryptophan decarboxylase in phenylketonuria. Their possible role in causing mental deficiency in the developing infant is discussed.

Jervis, George A.; Block, Richard J.; Bolling, Diana; and Kanze, Edna: Chemical and Metabolic Studies on Phenylalanine. II. The Phenylalanine Content of the Blood and Spinal Fluid in Phenylpyruvic Oligophrenia. JOURNAL OF BIOLOGICAL CHEMISTRY, 1940, 134, 105-113 (June).

Quantitative determinations of phenylalanine and of phenylpyruvic acid in the blood of 16 patients with phenylketonuria showed a content of phenylalanine varying from 15 to 41 mg. per 100 ml. and the absence of phenylpyruvic acid. Blood phenylalanine showed a significant increase following ingestion of proteins, phenylalanine, phenylpyruvic acid, and phenyllactic acid. Ingestion of phenylalanine produced an increase in phenylalanine in the spinal fluids of patients.

Jervis, George A.: Studies on Phenylpyruvic Oligophrenia. The Position of the Metabolic Error. JOURNAL OF BIOLOGICAL CHEMISTRY, 1947, 169, 651-656 (August).

Findings support the hypothesis that the error consists of a blockage in the conversion of phenylalanine into tyrosine. In normal individuals, but not in phenylketonurics, the ingestion of phenylalanine is followed by a temporary increase in the blood of tyrosine-reacting substances.

Jervis, George A.: Excretion of Phenylalanine and Derivatives in Phenylpyruvic Oligophrenia. PROCEEDINGS OF SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1950, 73, 83-86 (October).

Quantitative data are presented on the urinary excretion of phenylalanine, phenylpyruvic acid, and phenyllactic acid in 20 patients with phenylketonuria. The values show inconspicuous differences from patient to patient kept on similar diets. High protein diet or the ingestion of phenylalanine and phenylpyruvic acid results in an increased daily output of phenyl compounds.

Jervis, George A.: Studies on Phenylpyruvic Oligophrenia: Phenylpyruvic Acid Content of Blood. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1952, 81, 715-720 (December).

Studies show that in phenylpyruvic oligophrenia, phenylalanine and various of its derivatives are present in the blood. There appears to be no correlation between phenylalanine, phenylpyruvic and phenyllactic acid content and intelligence.

Jervis, George A.: Phenylpyruvic Oligophrenia Deficiency of Phenylalanine-Oxidizing System. PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1953, 82, 514-515 (March).

The demonstration of the absence of a specific enzyme clarifies the observation that phenylketonuria is determined by a single recessive gene. Patients with phenylketonuria cannot oxidize phenylalanine to tyrosine because this specific enzyme system is defective (or lacking). Liver extracts of two phenylketonuric patients failed to catalyze the conversion of phenylalanine to tyrosine.

Jervis, George A.: Pathogenesis of the Mental Defect. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 101-113).

The author, who has made important contributions to the development and understanding of phenylketonuria, critically reviews the various hypotheses which have been suggested to explain the still unknown causes of the mental defect and the mechanism by which this defect develops in children affected by this disease. He includes the following postulates: direct toxic effect of metabolites; interference of excess phenylalanine and derivatives with enzymatic systems; structural alterations of brain constituents; and amino acid unbalance.

Kaufman, Seymour: Studies on the Mechanism of the Enzymatic Conversion of Phenylalanine to Tyrosine: Implications for Phenylketonuria. CHEMICAL PATHOLOGY OF THE NERVOUS SYSTEM. (Proceedings of the Third International Neurochemical Symposium - Strasbourg, 1958) New York, N.Y.: Pergamon Press, 1961. pp. 51-55.

When the conversion of phenylalanine was shown to require two enzymes, it seemed reasonable to believe that a free intermediate (e.g. an "activated phenylalanine") might be found in the reaction. (The author found that one enzyme is almost non-functional in phenylketonuria; the other enzyme and a cofactor are present. The one that is not active in phenylketonuria is that one which is intimately involved in the hydroxylation reaction.) If one made the further assumption that it was the second enzyme in the sequence which was missing in phenylketonuria, this hypothetical intermediate could accumulate, and in abnormally high concentrations behave as a toxic compound.

The hydroxylation reaction itself has not yet been separated into two steps. While further work may achieve such a separation, there still is no evidence that a free intermediate is formed in the reaction. Therefore, although the idea of a toxic intermediate in phenylketonuria has a certain attraction, it is not supported by any of the recent work on the mechanism of this reaction.

Knox, W. Eugene: Pathogenetic Effects of Elevated Plasma Phenylalanine in Phenylketonuria. CHEMICAL PATHOLOGY OF THE NERVOUS SYSTEM. (Proceedings of the Third International Neurochemical Symposium.- Strasbourg, 1958) New York, N.Y.: Pergamon Press, 1961. pp. 32-36.

The author describes the pathogenesis of mental deficiency in homozygotes of phenylketonuria, including a discussion of the overflow of metabolites, inhibited and deficient tyrosine metabolism, amino acid imbalance, and defective biochemical maturation of the brain. He explains his reasons for believing that the major consequences of the disease appear to be the failure of the normal maturation of the brain, which is more or less irreversible. "We need to describe the normal enzymatic development of the brain and to determine the aberrations in phenylketonuria."

He points out that experimental analysis of phenylketonuria and its pathogenesis may now become possible as a result of the discovery of how to control the enzyme level in order to experimentally reproduce the disease in laboratory animals. The presence of phenylalanine hydroxylase in excess in the liver of all experimental animals had prevented reproduction of the disease until this recent development.

Kretchmer, Norman; and Etzwiler, Donnell D.: Disorders Associated with the Metabolism of Phenylalanine and Tyrosine. PEDIATRICS, 1958, 21, 445-475 (March).

Disorders of incomplete metabolism of phenylalanine and tyrosine are outstanding examples of gene-enzyme interrelationships. An over-all scheme of the metabolism of phenylalanine and tyrosine and the associated enzymatic blocks is summarized.

Meister, Alton; Udenfriend, Sidney; and Bessman, Samuel P.: Diminished Phenylketonuria in Phenylpyruvic Oligophrenia after Administration of L-Glutamine, L-Glutamate or L-Asparagine. JOURNAL OF CLINICAL INVESTIGATION, 1956, 35, 619-626 (June).

Two phenylketonuric patients were given single oral doses of L-glutamine, sodium L-glutamate, L-asparagine, glycine, sodium succinate or D-glucose, and the urinary excretion of phenylpyruvic acid was measured for several hours prior to and after administration of the test compound. Results of experimental studies are presented. Findings are discussed in terms of the concept that transamination plays a role in phenylpyruvic oligophrenia.

Meister, Alton: Phenylpyruvic Oligophrenia. PEDIATRICS, 1958, 21, 1021-1061 (June).

The article discusses the biochemical phenomena associated with phenylketonuria and reviews briefly the present status of knowledge concerning the intermediary metabolism of phenylalanine and tyrosine. The metabolic deficit appears to be primarily one of specific hepatic function. Studies thus far have dealt only with enzyme activity. A complete biochemical explanation of the cerebral defect is still lacking.

Pare, C. M. B.; Sandler, M.; and Stacey, R. S.: 5-Hydroxytryptamine Deficiency in Phenylketonuria. LANCET, 1957, 1, 551-553 (March 16).

The levels of 5-hydroxytryptamine in the serum and 5-hydroxyindoleacetic acid in the urine were assayed in children with phenylketonuria and in controls. Abnormally low levels of both were found in the phenylketonuric group.

Pare, C. M. B.; Sandler, M.; and Stacey, R. S.: Decreased 5-Hydroxytryptophan Decarboxylase Activity in Phenylketonuria. LANCET, 1958, 2, 1099-1101 (November 22).

The effect of a low-phenylalanine diet was studied in seven phenylketonuric children. There was a significant rise in the mean serum 5-hydroxytryptamine level under this dietary regime. After intravenous 5-hydroxytryptophan injection, 4 patients showed a lower urinary output of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid when compared with matched controls. These results suggest that 5-hydroxytryptophan decarboxylase might be inhibited by abnormal metabolites of phenylalanine in phenylketonuria.

Pare, C. M. B.; Sandler, M.; and Stacey, R. S.: The Relationship between Decreased 5-Hydroxyindole Metabolism and Mental Defect in Phenylketonuria. ARCHIVES OF DISEASE IN CHILDHOOD, 1959, 34, 422-425 (October).

The low serum 5-hydroxytryptamine and urinary 5-hydroxyindoleacetic acid previously reported in phenylketonuria has been confirmed in a larger series. For this study, 49 phenylketonuric patients and 32 mental defective controls were seen. Groups were comparable for weight, age and intelligence. There was a relationship between 5-hydroxyindole levels and intelligence.

Partington, M. W.: A Note on the Effects of Phenylalanine on the Blood Sugar in Phenylketonuria. JOURNAL OF MENTAL DEFICIENCY RESEARCH, 1961, 5, 1-3 (June).

Findings of this study showed that oral doses of phenylalanine produced a small but significant rise in the blood sugar. The increase occurred in patients with phenylketonuria as well as in other subjects (2 control groups of retarded children and normal adults). It follows that the seizure activity of untreated phenylketonuria is not related to a hypoglycaemic effect of phenylalanine. Hypoglycaemic convulsions have, however, been reported in phenylketonuric patients treated with a low-phenylalanine diet, presumably due to a general nutritional deficiency.

Partington, Michael W. and Lewis, Elizabeth J. M.: Variations with Age in Plasma Phenylalanine and Tyrosine Levels in Phenylketonuria. JOURNAL OF PEDIATRICS, 1963, 62, 348-357 (March).

Findings are based on fasting plasma phenylalanine levels of 72 patients with untreated phenylketonuria ranging in age from birth to 54 years. Highest phenylalanine levels were found in patients between 11 days and 10 months of age. Dietary studies of intake of phenylalanine indicated that this was largely due to the proportionally higher intake of phenylalanine at this early age period. The fasting plasma tyrosine level was found to be higher than normal in babies with phenylketonuria, whereas it was significantly lower than normal in older patients. The authors suggest that the important factor in the production of brain damage in the infant with untreated phenylketonuria may not be a peculiar vulnerability of the growing brain, but the degree of biochemical abnormality to which it is exposed.

Perry, Thomas L.: Urinary Excretion of Amines in Phenylketonuria and Mongolism. SCIENCE, 1962, 136, 879-880 (June 8).

Children with phenylketonuria excrete considerably less serotonin and tryptamine and somewhat less normetanephrine and p-tyramine than normal children. The excretion of these amines was not decreased in mongolism. Even during monoamine oxidase blockade, o-tyramine could not be detected in the urine of phenylketonurics. These findings are discussed in relation to the mental defect of phenylketonuria.

Reichle, Frederick A.; Baldrige, Robert C.; Dobbs, June; and Trompeter, Marianne: Tryptophan Metabolism in Phenylketonurics. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 1961, 178, 939-941 (December 2).

The levels of serotonin in the platelet-rich plasma of uncontrolled phenylketonurics are lower than are those of controlled phenylketonuric and of nonphenylketonuric children. Plasma hydroxyindole concentrations of a phenylketonuric child were found to increase when serum phenylalanine levels decreased, following dietary control.

The increments in plasma hydroxyindole concentrations following oral administration of L-tryptophan or DL-5-hydroxytryptophan were greater in uncontrolled phenylketonurics than in nonphenylketonuric children and in a controlled phenylketonuric. These findings support the hypothesis that, in phenylketonuria, elevated levels of phenylalanine or its metabolites may result in inhibition of the 5-hydroxytryptophan decarboxylase system.

Tashian, Richard E.: Phenylpyruvic Acid as a Possible Precursor of O-Hydroxyphenylacetic Acid in Men. SCIENCE, 1959, 129, 1553 (June 5).

In order to test for possible o-hydroxylation of phenylpyruvic acid or its metabolites, sodium salt of phenylpyruvic acid was orally administered to three normal, adult males. Results showed that ingestion of phenylpyruvic acid causes an increased urinary excretion of o-hydroxyphenylacetic acid (o-HPAA) and indicates that phenylpyruvic acid may be a precursor for o-HPAA. On the basis of these findings, it is not necessary to assume an increased production of o-tyrosine in phenylketonuria in order to account for the increase of o-hydroxy derivatives of phenylalanine.

Udenfriend, Sidney and Cooper, Jack R.: Assay of L-Phenylalanine as Phenylethylamine after Enzymatic Decarboxylation; Application to Isotopic Studies. JOURNAL OF BIOLOGICAL CHEMISTRY, 1953, 203, 953-960 (February).

A procedure for the assay of L-phenylalanine in tissues and protein hydrolysates is presented. A procedure also is presented for obtaining phenylethylamine enzymatically from amino acid mixtures containing phenylalanine, in sufficient quantity and purity for radioactive measurement.

Udenfriend, Sidney, and Bessman, Samuel P.: The Hydroxylation of Phenylalanine and Antipyrine in Phenylpyruvic Oligophrenia. JOURNAL OF BIOLOGICAL CHEMISTRY, 1953, 203, 961-966 (August).

3-C14-DL-Phenylalanine was administered orally to a dog, two normal adults, and two phenylketonuric children. The ratio of the activity of tyrosine to phenylalanine (T:P) was used as an index of the extent of conversion of phenylalanine to tyrosine. Significant values for T:P were found in the phenylketonurics. However, in the controls and in the dog, T:P values were 10 to 15 times greater. It is apparent that hydroxylation of L-phenylalanine to tyrosine does take place in the condition of phenylpyruvic oligophrenia, but to a diminished degree.

Woolf, L. I.: Excretion of Conjugated Phenylacetic Acid in Phenylketonuria. BIOCHEMICAL JOURNAL, 1951, 49, ix-x (June).

Phenylacetylglutamine, the conjugated form of phenylacetic acid, is present in large amounts in urine from phenylketonuric patients.

This indicates a metabolic pathway for phenylalanine which was hitherto undescribed.

Woolf, L. I. and Vulliamy, D. G.: Phenylketonuria with a Study of the Effect upon It of Glutamic Acid. ARCHIVES OF DISEASE IN CHILDHOOD, 1951, 26, 487-494 (December).

It is suggested that the mental and neurological effects of phenylketonuria are due to an intoxication by phenylalanine or its abnormal metabolites and that a diet low in phenylalanine should be worth investigation as a possible form of treatment. Administration of glutamic acid had no effect on the intelligence of two phenylketonurics. Clinical features of phenylketonuria are described and discussed.

Woolf, L. I.: Recent Work on Phenylketonuria and Maple Syrup Urine Disease. PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, 1962, 55, 824-826 (October).

The theory that the clinical effects of phenylketonuria are due to an intoxication by phenylalanine or its abnormal metabolites, and that a diet low in phenylalanine can be beneficial, has been confirmed in the 11 years since this was put forward. A similar theory seems to apply to maple syrup urine disease (leucinosis). A marked deficiency of myelin is a feature of both diseases and active demyelination is found in some phenylketonurics. Some of the metabolites of phenylalanine and leucine are known to affect enzymes synthesizing synaptic transmitters. These effects on synaptic transmitters and on myelin must be combined into a single theory in considering the relationship between the metabolic error and the mental and neurological features of these two diseases.

CLINICAL AND PATHOLOGICAL FINDINGS

Alvord, Ellsworth C., Jr.; Stevenson, Lewis D.; Vogel, F. Stephen; and Engle, Ralph L., Jr.: Neuropathological Findings in Phenylpyruvic Oligophrenia (Phenylketonuria). JOURNAL OF NEUROPATHOLOGY, 1950, 9, 298-310 (July).

An examination was made of the central nervous system of five cases that had clinical manifestations of phenylketonuria. A marked lack of myelinization of the nervous system involving principally the optic, cortico-spinal, cortico-ponto-cerebellar, and possibly other tracts in the central and peripheral nervous system, was found in siblings of 16 months and $5\frac{1}{2}$ years of age. In one case of an adult, a defect in myelinization was noted in the optic chiasm; two other adult cases showed no such change anywhere. Other abnormalities, however, such as gliosis and increase of fat about blood vessels, were present in all 5 cases. The question is raised as to whether the retardation in myelinization may be at least in part responsible for the mental deficiency.

Cowie, Valerie, and Penrose, L. S.: Dilution of Hair Color in Phenylketonuria. ANNALS OF EUGENICS, 1951, 15, 297-301 (March).

Hair color in phenylketonurics, studied by reflectograms, is shown to be significantly lighter than that of their unaffected sibs. The degree of hair pigmentation was found to increase with age more slowly in phenylketonuria than in a control population.

Crome, L. and Pare, C. M. B.: Phenylketonuria: A Review and a Report of the Pathological Findings in Four Cases. JOURNAL OF MENTAL SCIENCE, 1960, 106, 862-883 (July).

Following a general review of the literature, the authors summarize neuropathological reports for 20 phenylketonuric cases. They then present their own clinical and pathological findings in four cases. Micrencephaly and fibrous gliosis of the white matter were main findings, but slight pallor of myelin staining was also demonstrated in two of the cases. The neuropathological, clinical and biochemical findings in phenylketonuria are compatible with the view that irreversible changes occur in the brain, but may only develop postnatally. This emphasizes need for early and effective treatment.

Diedrich, William M., and Poser, Charles M.: Language and Mentation of Two Phenylketonuric Children. JOURNAL OF SPEECH AND HEARING DISORDERS, 1960, 25, No. 2, 124-134 (May).

Two siblings with congenital aphasia, and who were later diagnosed as having phenylketonuria, are reported. During 3 years of control on a phenylalanine-low diet, there was marked improvement in language as well as in functional mentation. Of particular interest was the fact that the diet was not initiated until the subjects were four and three years of age respectively. It is suggested that speech pathologists be aware of phenylketonuria as a possible cause of delayed language development in children who otherwise may appear near normal.

Feinberg, S. B. and Fisch, R. O.: Roentgenologic Findings in Growing Long Bones in Phenylketonuria. Preliminary Study. RADIOLOGY, 1962, 78, 394-398 (March).

In a group of 33 patients with phenylketonuria studied at the University of Minnesota Hospitals, five in the younger age range who had been on restricted diets exhibited unusual bone changes in growing long bones. Four of the older patients who were not on restricted diets displayed moderately positive findings. One showed the first bone change after the age of four, when he was placed on a restricted diet.

The characteristic abnormality is fully described. The investigators hope that studies in progress will further the understanding of the underlying metabolic mechanisms and determine whether they are related to specific essential amino acid deficiencies.

Fleisher, T. Lawrence and Zeligman, Israel: Cutaneous findings in Phenylketonuria. A.M.A. ARCHIVES OF DERMATOLOGY, 1960, 81, 898-903 (June).

Cutaneous findings, during 8 years of observation, are reported for 23 phenylketonuric patients who were in a State institution for mental defects. All were white, non-Jewish, 2 years of age or older, and severely retarded. All subjects were found to have fair skin and light hair and 19 had blue eyes. Atopic dermatitis was present in 3 patients. Atopic intradermal skin test responses were present in 10 of 21 phenylketonuric subjects, and in only 4 of 21 controls.

"More or less diffuse eczema" was early reported to be a common accompaniment of phenylketonuria and it has continued to appear in case reports of this disease. The authors believe that use of the term "eczema" is unfortunate. The multiple uses of this term prohibit a universally accepted definition and it is an indefinite terminology which does not mean the same thing to different investigators. "Infantile eczema" is almost as indefinite, and embraces a group of diseases rather than any definite cutaneous disease.

Fois, Alberto; Rosenberg, Carl; Gibbs, Frederic A.: The Electroencephalogram in Phenylpyruvic Oligophrenia. ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, 1955, 7, 569-572 (November).

EGG studies in the waking and sleeping state of 19 patients with phenylketonuria reveal that waking activity in these patients is usually abnormal; it is of high voltage, slightly fast, slightly slow, or a mixture of fast and slow; seizure discharges of the petit mal type are common. Eleven patients showed seizure activity in the waking state and 18 had seizure activity during sleep. Thus EEG confirms the clinical observation that epileptic disorder is a common complication in this disease. Findings of these EEG studies suggested a pathological process with a strong epileptic component, causing a profound disturbance of both cortical and thalamic function.

French, Joseph H.; Clark, David B.; Butler, Harry G.; and Teasdall, Robert D.: Phenylketonuria: Some Observations on Reflex Activity. JOURNAL OF PEDIATRICS, 1961, 58, 17-22 (January).

Low threshold H reflexes were recorded from the anterolateral muscles in 5 of 12 patients with phenylketonuria. A similar incidence was noted in patients with a congenital or infantile hemiparesis. It is believed that the enhancement of this reflex activity is related to damage of developing pathways within the central nervous system.

Herrlin, Karl-Magnus: A Clinical and Electroencephalographic Study of a Pair of Monozygotic Twins with Phenylketonuria. ACTA PAEDIATRICA, 1962, 51 (Suppl. 135), 88-96 (June).

A pair of monozygotic male twins with untreated phenylketonuria, born in 1943, were studied clinically and with EEG. Mental retardation and epilepsy were observed simultaneously in both twins at a few months of age and at 2½ years respectively their oligophrenia, epilepsy, and EEG findings showed appreciable differences. One twin has an IQ of 55 and 3/sec. spike and wave epilepsy, whereas the other has an IQ of 26 with epilepsy of a focal type. The only known lesion factor is their metabolic disturbance. Thus it appears that their brain damages differ in type and degree of severity, although the metabolic disturbances could be expected to be equally pronounced in both and the reaction norms of their brain tissue the same, since they are genetically identical. These findings indicate that differences in cerebral dysfunction, including oligophrenia in phenylketonurics, may depend more on random differences in the extent and localization of the cerebral lesions than on variations in genetic constitution.

Jervis, George A.: The Clinical Picture. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 52-61).

The author reviews knowledge available about the signs and symptoms of phenylketonuria. He divides his presentation into three major fields: (1) mental manifestations, consisting mainly of intellectual retardation; (2) neurological abnormalities, including epilepsy, muscular hypertonicity and motor impairment; and (3) extraneural manifestations, including defect in pigmentation, skin lesions, body size, height and weight, and body odor.

Jervis, George A.: Pathology. [In] PHENYLKETONURIA, edited by Frank L. Lyman. Springfield, Ill.: Charles C Thomas, 1963. 318 pp. (p. 96-100).

Reported findings on brain weight, myelin changes and gliosis in about 25 cases of phenylketonuria are summarized and evaluated. The author points out that present information on morphological lesions is scanty and somewhat contradictory. "There is indeed a baffling

discrepancy between the severity of the clinical picture and the mildness of pathological lesions. One is tempted to conclude that the basic lesion is at a chemical level not detectable by the present methods of morphological investigation."

Kratter, Frederick Edward: The Physiognomic, Psychometric, Behavioral and Neurological Aspects of Phenylketonuria. JOURNAL OF MENTAL SCIENCE, 1959, 105, 421-427 (April).

Twelve cases of untreated phenylketonuria are described. Tables in text present systematically classified information for each of the 12 cases in relation to physical characteristics, behavioral responses during psychometric test interview, psychological examination test results, family history, and developmental data.

All cases were blond and all but one were blue-eyed. Practically all cases showed distractibility and extreme short-lived span of attention and interest in surroundings. Of the 12 cases, 9 fell within range of severe mental deficiency and 3 had an IQ ranging from 20 to 37. Repeated psychological tests showed slow but discernible growth in mental age of 5, no change in 3, and loss in 4. Social and developmental histories showed a pronounced lag in their maturational growth and a frequent incidence of psychological and clinico-pathological findings in their family histories. Neurological data indicated an involvement of the pyramidal, striatal and cerebellar systems.

Little, Scott W.: Suspected Hearing Defects in Phenylketonuria. ARCHIVES OF OTOLARYNGOLOGY, 1962, 75, 515-518 (June).

Two cases are presented in which the presumptive diagnosis of phenylketonuria was first made by the author, an otolaryngologist. Both children were brought to him by their parents with complaints of suspected hearing difficulty. On basis of his examination and clinical observations of each of these children, the author suspected phenylketonuria. In both cases, ferric chloride tests were carried out and diagnosis was confirmed by phenylalanine blood determinations. Provision was made immediately for pediatric care and dietary treatment. Though no hearing difficulty was discovered, a detectable and treatable mental deficiency was revealed. The author recommends that in the ancillary investigation of hearing in young children, one of the screening methods for detection of phenylketonuria should be utilized routinely.

Low, Niels L.; Bosma, James F.; and Armstrong, Marvin D.: Studies on Phenylketonuria. VI. EEG Studies in Phenylketonuria. A.M.A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 1957, 77, 359-365 (April).

Results reported in this paper confirm findings of other investigators that nearly all untreated phenylketonuric patients show electroencephalographic abnormalities. In this particular series, a considerable

number of recordings were made on patients of much younger age than had previously been studied. The younger patients, in general, demonstrated more severe abnormalities than were seen in older patients.

EEG study was made of eight patients on phenylalanine-restricted diet. In most cases in which there have been conspicuous EEG abnormalities, with or without apparent clinical seizures, the EEG's have been improved and in some cases normalized. In three out of five cases with clinical seizures, the seizures ceased to occur.

Partington, Michael W.: The Early Symptoms of Phenylketonuria. PEDIATRICS, 1961, 27, 465-473 (March).

The early clinical histories of 36 patients with phenylketonuria were studied. It was found that more than half the patients had suffered from symptoms of one sort or another in the early weeks of life. They began months before any sign of mental defect was evident to the parents. The main symptoms were vomiting (17 patients), irritability (12 patients), seizures (13 patients) and eczema (6 patients). It is recommended that all infants having these symptoms should be tested for phenylketonuria.

Poser, Charles M. and Van Bogaert, L.: Neuropathologic Observations in Phenylketonuria. BRAIN, 1959, 82, 1-9 (March).

Neuropathologic examination of the brain of an 18-year-old patient with phenylketonuria revealed multiple areas of altered myelination associated with variable degrees of fibrillary gliosis. Neuropathologic observations, together with a review of the literature, indicate that this disease should be classified with the leucodystrophies and the cerebral lipidoses in the general group of demyelinating diseases.

Shizume, K. and Naruse, H.: Dilution of Hair Colour in Japanese Children with Phenylketonuria. JOURNAL OF MENTAL DEFICIENCY RESEARCH, 1958, 2, 53-54 (December).

As all Japanese normally have black hair, the brown hair color of the Japanese child pictured with a normal child in this article, seems to give good evidence of dilution of hair color in phenylketonuric patients. The affected child's skin also is lighter and her eyes show slight dilution of color.

The following list of references is provided for the reader who is interested in experimental production of phenylketonuria:

- Auerbach, Victor H.; Waisman, Harry A.; Wyckoff, L. Benjamin: Phenylketonuria in the Rat Associated with Decreased Temporal Discrimination Learning. NATURE, 1958, 182, 871-872 (September 27).
- Cadell, T. E.; Harlow, H. F.; Waisman, H. A.: EEG Changes in Experimental Phenylketonuria (Monkeys). ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, 1962, 14, 540-543 (August).
- Freedland, R. A.; Krakowski, M. C.; and Waisman, Harry A.: Influence of Dietary Aromatic Amino Acids on Phenylalanine Hydroxylase Activity (Rats). FEDERATION PROCEEDINGS (Federation of American Societies for Experimental Biology), 1960, 19, 7 (March).
- Goldstein, F. B.: Biochemical Studies on Phenylketonuria. I. Experimental Hyperphenylalanemia in Rats. JOURNAL OF BIOLOGICAL CHEMISTRY, 1961, 236, 2656-2661 (October).
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